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ORGANIC SEMINAR ABSTRACTS

1980-81, Semester I

University of Illinois

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ORGANIC SEMINAR ABSTRACTS

1980-81, Semester I

University of Illinois

School of Chemical Sciences

Department of Chemistry

University of Illinois

Urbana, Illinois

61801

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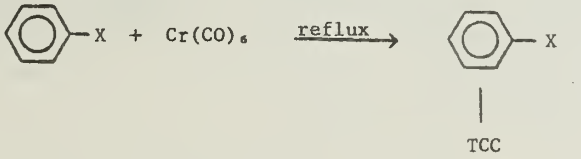
η^6-Arenetricarbonyl-chromium(0) Complexes in Organic Synthesis

Reported by Daniel Dess September 4, 1980

Introduction. Reactions that interchange or introduce substituent groups on aromatic rings are very important in organic chemistry. The most common method for introducing a substituent is electrophilic aromatic substitution. Nucleophilic aromatic substitution is also important. This method requires that a leaving group be present on the ring and usually requires that some electron withdrawing group also be present.[1] Recently it has been observed that coordination of a chromium tricarbonyl unit to an aromatic ring via Π bonding increases the reactivity of the ring toward attack by nucleophiles.[2,3] Unlike activating groups used in classical nucleophilic aromatic substitution, the chromium tricarbonyl unit is easily attached and removed.[2,3] These η^6-arenetricarbonylchromium(0) (η^6-arene TCC) complexes have shown promise as useful reagents for the introduction of alkyl substituent groups on aromatic rings. This report will present the scope and limitations of this reaction and proposed mechanisms. Methods for synthesizing η^6-arenetricarbonylchromium will also be outlined.

Preparation of η^6-Arenetricarbonylchromium(0) Complexes. η^6-benzenetricarbonylchromium was synthesized for the first time by combining dibenzene chromium and chromium hexacarbonyl in benzene in a sealed system at 220°.[4] A simpler method has since been devised (Eq. 1) in which chromium hexacarbonyl (2) and the aromatic compound (1) are heated at reflux at atmospheric pressure in diethylene glycol dimethyl ether, decalin or di-n-butyl ether[3,5] (Eq. 1). The reacting aromatic compound has also been used as the solvent. Aromatic



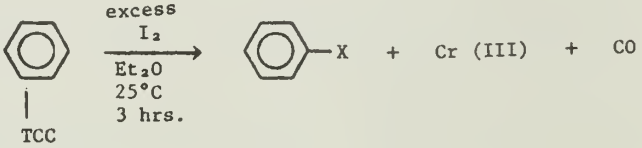
(1)

1 2 3

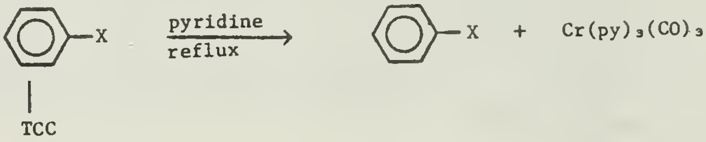
	X		yield(%)
1a,	H	3a	30
b,	CH_3	b	80
c,	OCH_3	c	94
d,	NH_2	d	91
e,	Cl	e	52
f,	$COCH_3$	f	35

compounds containing electron withdrawing substituents usually do not give good yields of η^6-arene TCCs.[3] Aromatic compounds with para substituents generally give poor yields also.[3]

η^6-Arene TCC are stable in air, and do not react rapidly with aqueous base or acid or reducing agents such as lithium aluminum hydride.[3] Reaction with mild oxidizing agents such as manganese dioxide, ceruim (IV), and iodine regenerates the aromatic compound, chromium (III) species, and carbon monoxide[3] (Eq. 2). Reaction of the complexes with refluxing pyridine also regenerates the aromatic compound[7] (Eq. 3).



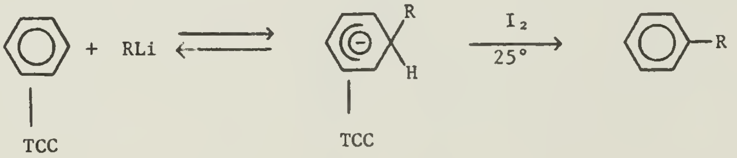
3 1 (2)



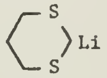
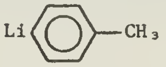
3 1 (3)

The pKa of Cr(CO)$_3$C$_6$H$_5$COOH is 4.77. The pKa of p-nitro benzoic acid is 4.48.[3] Thus the tricarbonyl chromium group exerts an electron withdrawing effect comparable to a para nitro group.

Reactions of η^6-Arene TCCs. η^6-Arene TCCs owe their synthetic utility to the fact that the chromium tricarbonyl unit is electron withdrawing[3,6] and thus activates the ring to nucleophilic addition.[6,8,9,10] Organolithium compounds react with 3a at 0°C in THF or THF/HMPA to give η^5-cyclohexadienyl TCCs,[6,8,11]



3a 4 5 6 (4)

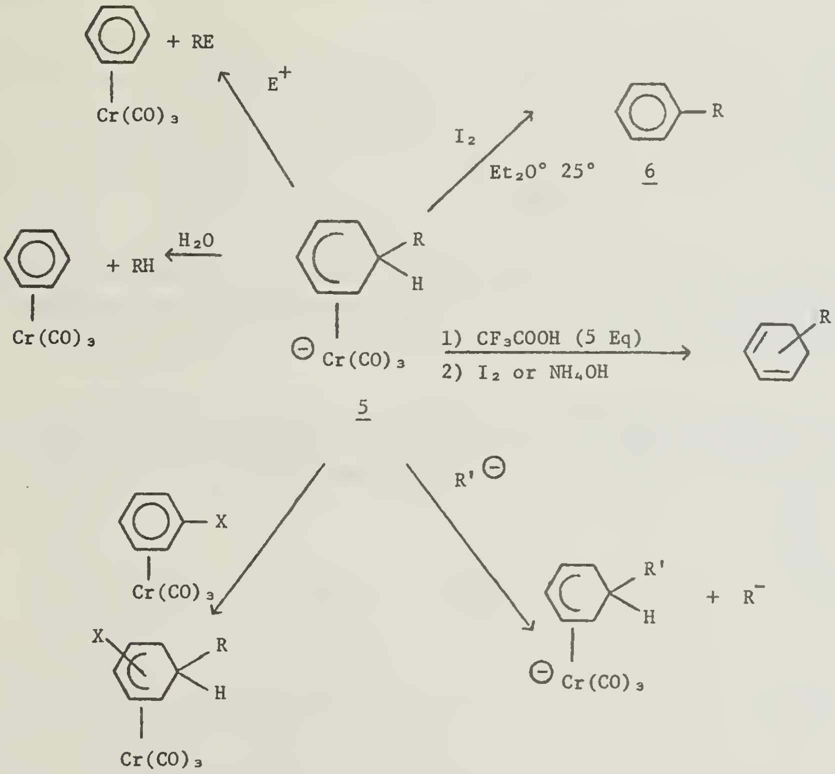
	Carbanion (4)	Product (6)	yield (%)
a		6a	93
b	Li(CH$_3$)$_2$CCN	6b	94
c		6c	71
d	LiC(CH$_3$)$_3$	6d	97
e	LiCH$_2$COO-t-Bu	6e	87

5 (Eq. 4). These complexes are stable in solution under an inert atmosphere for long periods when kept at or below 0°C.[6,8] They decompose rapidly upon exposure to water or oxidizing agents.

The proposed structure of the complexes is based on ^{1}H NMR spectra for several different R groups.[6,8] When R is 1,3-dithianyl, 5a is stable enough to isolate as a crystalline solid. X-ray diffraction studies of the crystal have confirmed the structure 5a.[6]

Complex 5 undergoes several interesting reactions as illustrated in scheme 1. Addition of I_2 to a solution of 5 in ether at 25°C gives the free aromatic ligand and chromium (III) species.[3,7,8,11] The two step conversion of 3 to 6 is equivalent to formal nucleophilic displacement of hydride (Eq. 4). This sequence has been found to be a convenient method for synthesizing a wide variety of alkyl substituted aromatic compounds.[2,6,9,10,12,13] Organolithium compounds that have been found to add to η^6-benzene TCC in high yield include the lithium salts of esters, nitriles, 1,3-dithiane acetals, and cyanohydrin-acetals.[6,9]

Scheme I



Anomalous results have been reported for the reaction of n-butyl lithium and η^6-arene TCCs.[12,13,14] While other carbanions added to the Π system of the arene, including tert-butyl lithium,[10] n-butyl lithium acted as a base producing the lithiated species 7 (Eq. 5). Electrophiles

Metathetical Reactions of Trivalent Pnictogens

Reported by Scott Anthony Culley September 11, 1980

A metathetical reaction is simply an exchange of ligands or cationic and anionic pairs between atomic centers. The central atoms may be of the same element, same family, or different families. The exchanging ligands may be identical or distinct. Metathetical reactions are also referred to in the literature as exchange, redistribution, scrambling, reorganization and disproportionation reactions.[1] The general scheme is given in Equation one, while specific metathetical reactions are seen in Equations two through five.

$$R_nP_N + R'_mP'_N \rightleftharpoons R'_xR_{n-x}P_N + R_xR'_{m-x}P'_N \qquad (1)$$

$(P_N = \text{pnictogen})$

$$\text{trivalent} : R_3P_N + R'_3P_N \rightleftharpoons R_{3-x}R'_xP_N + R_xR'_{3-x}P'_N \qquad (2)$$

$$\text{pentavalent}: R_5P_N + R'_5P'_N \rightleftharpoons R_{5-x}R'_xP_N + R_xR'_{5-x}P'_N \qquad (3)$$

$$\text{mixed} : R_3P_N + R'_5P_N \rightleftharpoons R'_2R_3P_N + R'_3P'_N \qquad (4)$$

$$\text{redox} : 3R_nP_NX_{3-n} + (5-n)R'_3P'_N \rightleftharpoons 3R'_{5-n}R_nP_N + 2P^{\circ}_N + (3-n)P'_NX_3 \qquad (5)$$

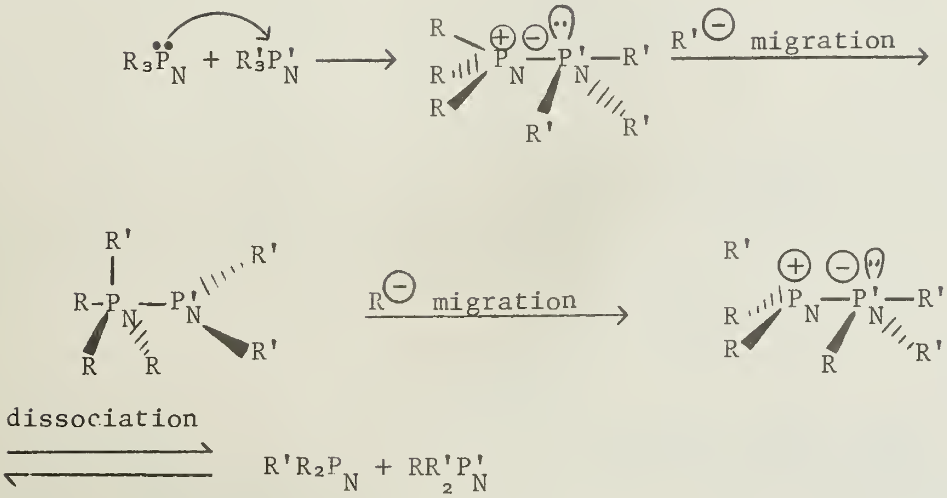
Although this review will focus upon metathetical reactions of trivalent pnictogens (group V elements) almost every family from the alkaline earths to the halogens exhibit some metathetical behavior. Metathetical reactions within the group V family provides a facile route to the substituted pnitides and in particular to the pnictogen halides. These compounds may then be allowed to react with various metals, grignard reagents, and organolithium compounds to yield symmetric or unsymmetric species ($R_1R_2R_3Bi$ not yet known). These trivalent species may then be allowed to react with various reagents to yield tetra, penta, and hexacoordinate pnictogens. In addition fluorophosphines which are easily prepared by metathetical reactions are finding wide use as coordinating ligands in transition metal complexes.[2,3,4,5,6]

Mechanisms. Various pathways for metathetical reactions have been suggested.[7] These are summarized in Schemes I and II.

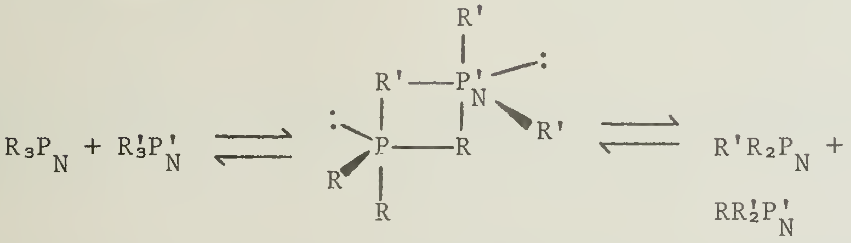
The available kinetic data[8,9,10,11] (mainly for antimony and arsenic) are summarized in Table 1. These data for an overall second order exchange reaction rules out most dissociative types of mechanisms since these would be first order. A second order dissociative mechanism is possible, however, if the second step is rate determining. Early workers[8,9] in this field have studied the disproportionation of diphenylchloroarsine and phenyldichloroarsine. The $\Delta S^{\neq}$ for these reactions is of the correct magnitude for a two center mechanism, but falls appreciably below that for suspected four center mechanisms.[12]

Scheme I. Associative

1. Biphilic:

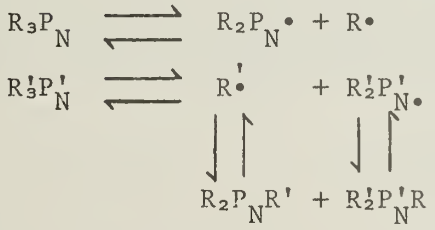

R'⊖ migration
R⊖ migration
dissociation

2. Four Center Mechanism:

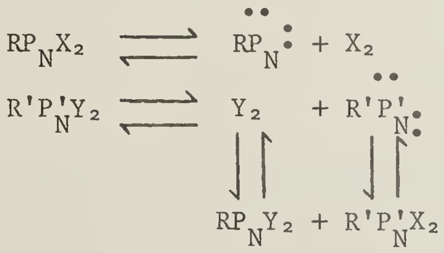


Scheme II. Dissociative

1. Radical, cationic, anionic: (only radical shown)



2. Elimination of halogen



3. Charge transfer:

$$R_3P_N + R'_3P'_N \rightleftharpoons \overset{+\bullet}{R_3P_N} + \overset{-\bullet}{R'_3P'_N}$$

$$\overset{+\bullet}{R_3P} \rightleftharpoons R^{\oplus} + \overset{\bullet}{R_2P_N}$$

$$R^{\oplus} + \overset{-\bullet}{R'_3P'_N} \rightleftharpoons \overset{\bullet}{RR'_3P'_N}$$

$$\overset{\bullet}{RR'_3P'_N} \rightleftharpoons RR'_2P'_N + \overset{\bullet}{R'}$$

$$\overset{\bullet}{R_2P_N} + \overset{\bullet}{R} \rightleftharpoons R'R_2P_N$$

Van Wazer[10] has studied the metathetical reactions of arsenic by n.m.r. and has found the fastest exchange at arsenic centers ($k = 10^2$ l./sec.-mol.) occurs between halogen and dimethylamino substituents while exchange between

Table 1

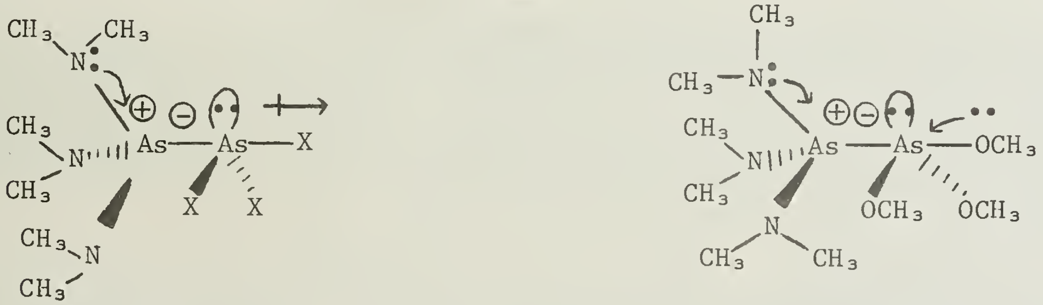
$$2\emptyset_2AsCl \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \emptyset_3As + \emptyset AsCl_2 \qquad \text{(neat)}$$

$$2\emptyset AsCl_2 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \emptyset_2AsCl + AsCl_3 \qquad \text{(neat)}$$

$k \times 10^3$ (cc/sec.-mol.)	E* (kcal./mol.)	ΔS* (e.u.)	ref.
k_1 = .89 (T = 252°C)	$E_1^* = 37.6$	$\Delta S_1^* = -2.88$	8
k_2 = 15.1 (T = 252°C)	$E_2^* = 34.0$	$\Delta S_2^* = -4.26$	8
k_3 = 3.22 (T = 256°C)			8
k_4 = 56.6 (T = 256°C)			8

dimethylamino and methoxyl substituents is too slow to measure by n.m.r. line broadening techniques. This absolute order of reactivity seems to support a biphilic mechanism (at least for this element) since the fastest rate is observed for a good nucleophile, trisdimethylaminoarsine, reacting with a good electrophile, an arsenic trihalide. The slowest rate is observed for the reaction of two good nucleophiles with each other. The proposed intermediate in the biphilic reaction mechanism is a zwitterionic species. Since the transition state most likely lies late along the reaction coordinate it would be closest in energy to the zwitterionic intermediate. Features which stabilize the intermediate would be expected to also stabilize the transition state more than the starting materials and thus increase the rate of the reaction. The zwitterionic intermediates are seen in Figure 1.

Figure 1

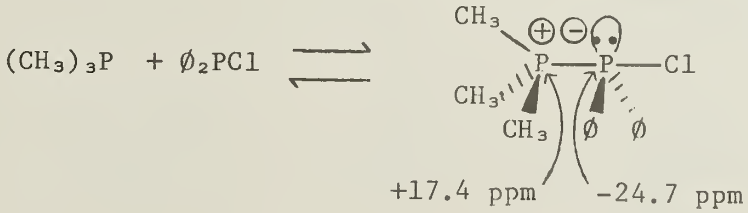


stabilized

destabilized

Further evidence for a biphilic mechanism comes from the reactions of trialkyls of phosphorous and arsenic with organophosphines and arsines. Several authors[13,14,15,16,17] have examined these reactions and report the isolation of crystalline adducts postulated to be salts of the general formula $[R_2P_{N}P'_{N}R_3]X$. The exact nature of bonding in these adducts is unclear. Ramirez[16] has reported the isolation of a solid material from the reaction of trimethylphosphine with diphenylchlorophosphine. Although he postulates an ionic structure the reported ^{31}P n.m.r. data are also consistent with a phosphonium phosphoranide (the intermediate in the biphilic mechanism). This species and the appropriate n.m.r. data are shown in Figure 2. Unfortunately no conductance measurements were reported. The X-ray crystal structure of this 1:1 adduct

Figure 2



1:1 adduct, 2.5 M CH_2Cl_2; shifts relative to H_3PO_4 where positive sign indicates downfield shift.

has not yet been reported. Many other examples of arsonium and phosphonium salts are reported in the literature, however, at least in the cases of mono and dihalo pnictogen adducts the evidence does not support an ionic structure. The melting points are surprisingly low and solutions of some of the species have relatively low conductances. For example methyldichloroarsine and trimethylarsine react to give a solid which has a specific conductance of only 5.6 μmho/cm. (10^{-3} M in nitromethane) and a melting point of 94-97°C.[14] It is probably best formulated as a zwitterionic compound.

Despite the fact that the nature of bonding in these species is uncertain, it seems clear that the phosphorus and arsenic centers are acting both as a nucleophile and an electrophile and the ability of the substituents to metathesize depends in part on their ability to enhance electrophilic or nucleophilic character at the metathetical center.

Antimony: A Four Center Exchange. Van Wazer[11] has studied the exchange reaction between trimethylstibine and trichloroantimony by NMR. The second order rate constants obtained in dimethylformamide at 72°C and 100°C were determined as well as the enthalpy and entropy of activation. The low entropy of activation (-25 e.u.) has been attributed to a four-center transition state. This $\Delta S^{\ddagger}$ is in accord with that of other four-center transition states.[12]

Thermodynamics. The available thermodynamic data (summarized in Table 2) indicate that almost all of the mixed products of metathetical reactions are favored to a greater extent than random exchange would predict. When the exchanging substituents on the pnictogen center are of the same class (*i.e.*, both alkoxy groups) the equilibrium lies closest to a completely random equilibrium. When the exchanging substituents are of different classes, quite significant deviations from random exchange are observed. For example, in the dimethylaminofluorine system the equilibrium constant is 6.9 x 10.[9]

Table 2

$$R_3P_N + R'_3P'_N \rightleftharpoons R'R_2P_N + RR'_2P'_N$$

System	R	R'	K	Reference
Statistical	—	—	9	18
P	OCH_3	OC_2H_5	6.9	19
	Cl	Oϕ	5.9×10^{1}	20
	$(CH_3)_2N$	Oϕ	4.2×10^{5}	21
	Cl	OC_2H_5	4.8×10^{5}	21
As	$(CH_3)_2N$	OCH_3	3.3×10^{1}	10
	Cl	OCH_3	1.6×10^{4}	10
	$(CH_3)_2N$	F	6.2×10^{9}	10

Survey of Synthetically Useful Metathetical Reactions: Phosphorus. Numerous metathetical reactions between trivalent phosphorus compounds are known. Trihalophosphines metathesize although only mixed halophosphines containing fluorine are isolable.[22] This may be due to the greater stability of the phosphorus fluorine bond (P-F > P-Cl > P-Br > P-I)[23] and the slower exchange rate of mixed halophosphines containing fluorine.[24] Phosphorus trihalides metathesize with other phosphorus trihalides or other pnictogen trihalides to yield mixed halo- and pseudohalophosphines. Some of the phosphines which may be obtained by this route are PF_2Br, $PFBr_2$, PF_2Cl, $PFCl_2$, $PF_2(NCO)$, $PF(NCO)_2$, and $PF_2(NCS)$.[25] A recent synthesis[3] which provides a very convenient method of generating the gaseous chlorodifluorophosphine is outlined in Equation 6.

$$(C_2H_5)_2N{-}PCl_2 \xrightarrow[\text{or}\ NaF]{SbF_3} (C_2H_5)_2NPF_2 \xrightarrow{PCl_3} ClPF_2 \tag{6}$$

Although trialkylphosphines (perfluoroalkyls are an exception, vide infra) have not been observed to metathesize with any pnictogen, dihalophosphines disproportionate to yield the monohalophosphine,[26]

Arsenic and antimony trifluoride have found wide use as metathetical fluorinating agents. These reagents metathesize with phosphorus trichloride either in the presence or absence of a catalyst to produce good yields (ca. 85%) of phosphorus trifluoride[27,28] as seen in Equation 7. These reagents also fluorinate dialkylamino and alkoxychlorphosphines as well as halophosphines with electronegative alkyl substituents in good yields (Equation 8). These reactions have been extensively reviewed by Schmutzler.[2,24,29]

$$PCl_3 \xrightarrow[\text{(cat.)}]{AsF_3,\ SbF_3} PF_3 \tag{7}$$

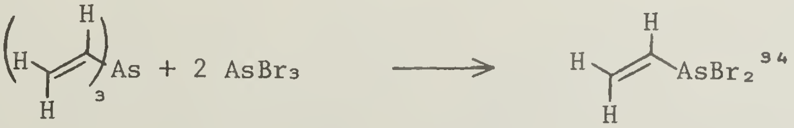
$$(CF_3)_2PI \xrightarrow{SbF_3} (CF_3)_2PF\ \text{[30]} \tag{8}$$

Although trialkylphosphines do not metathesize, tris(trifluoromethyl)phosphine does metathesize. Emeléus indirectly observed this behavior in the reaction of white phosphorus with iodotrifluoromethane.[31] Direct observation came later with the metathetical reaction of tris(trifluoromethyl)phosphine and trimethylbismuthine.[32]

Arsenic. Unlike phosphorus, mixed haloarsines have not yet been isolated. This is probably due to the faster exchange rates of arsenic. Also unlike phosphorus, exchange reactions of trialkylarsines are known as seen in Equations 9, 10, and 11. Triarylarsines generally react with arsenic trichloride to give aryldichloroarsines.[33]

$$(C_2H_5)_3As + 1.25\ AsBr_3 \longrightarrow (C_2H_5)AsBr_2\ \text{[34]} \tag{9}$$

51%



(10)

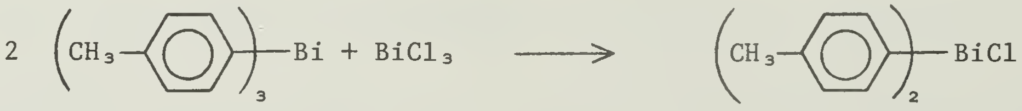
38%

$$(CF_3)_3As + 2\ AsCl_3 \longrightarrow (CF_3)AsCl_2\ \text{[35]} \tag{11}$$

50%

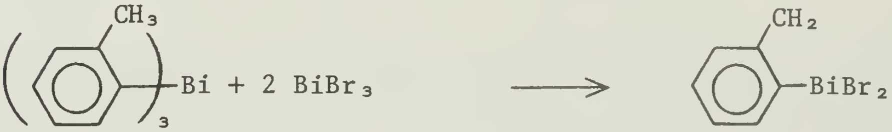
Antimony. The fast rate of exchange for trivalent antimony compounds generally makes isolation of liquid metathesis products difficult. Another difficulty arises from the similar physical properties (boiling and melting points) of the metathesis products. Thus, when trivinylstibine and antimony tribromide were mixed in a 1:2 ratio, the desired dibromo compound could not be obtained.[34] Only the divinyl derivative could be isolated in pure form.[34] However, successful metathetical reactions between various stibines and antimony trihalides have been reported.[36,37]

Bismuth. Bismuth seems to be the most reactive of the pnictogens in metathetical reactions. Thus, while triarylantimony, arsenic, and phosphorus compounds require high (ca. 240°C) temperatures, triarylbismuthines react at room temperature in ethereal solvents.[38] These are summarized in Equations 12, 13, and 14.



(12)

93%



(13)

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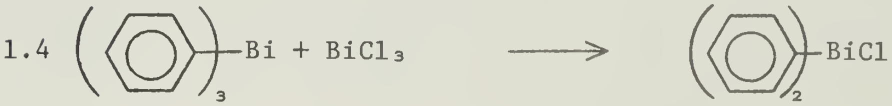


(14)

99%

Redox Reactions. Not all trivalent pnictogens undergo metathetical reactions. In some cases, disproportions are observed. Challenger was one of the first to observe this behavior when he mixed triphenylstibine with antimony trichloride as in Equation 15.[39]

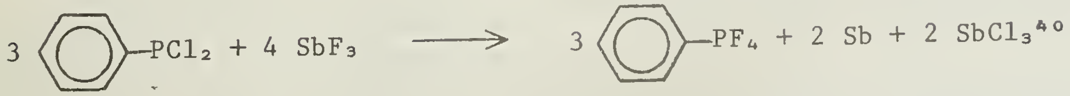
$$\phi_3Sb + BiCl_3 \longrightarrow \phi_3SbCl_2 + Bi_2Cl_4 \qquad (15)$$

Schmutzler[29] has extensively studied the reactions of chlorophosphines with antimony and arsenic trifluoride which leads to the fluorophosphoranes according to Scheme III. These reactions usually give good yields of the phosphorane (Equation 16), however, phosphines R_xPX_{3-x}, where $R = R_f$, NR_2, or OR yield only the fluorinated phosphine as previously mentioned.

Scheme III

$$3\ R(Ar)PCl_2 + 4\ P_NF_3 \longrightarrow 3\ R(Ar)PF_4 + 2\ P_N^{\circ} + 2\ P_NCl_3$$

$$3\ R_2(Ar_2)PCl + 3\ P_NF_3 \longrightarrow 3\ R_2(Ar_2)PF_3 + 2\ P_N^{\circ} + P_NCl_3$$



(16)

83-87%

Sisler has extensively studied the reactions of trialkyl pnictogens with mono-, di-, and trihalo pnictogens.[13,14] These reactions yield the pentavalent pnictogen and some form of the reduced pnictogen as seen in Equations 17-19. These reactions proceed, in many cases, through an isolable adduct which may be thermally converted to the pentavalent species.

$$3\ (n\text{-}C_4H_9)_3P + 2\ PCl_3 \longrightarrow 3\ (n\text{-}C_4H_9)_3PCl_2 + 2\ P^{\circ} \qquad (17)$$

$$5\ (n\text{-}C_4H_9)_3P + 5\ \phi PCl_2 \longrightarrow 5\ (n\text{-}C_4H_9)_3PCl_2 + (\phi P)_5 \qquad (18)$$

$$(n\text{-}C_4H_9)_3P + 2\ \phi_2PCl \longrightarrow (n\text{-}C_4H_9)_3PCl_2 + \phi P\text{-}P\phi_2 \qquad (19)$$

Redox vs. Metathesis. The factors controlling whether two trivalent pnictogens will metathesize or react in a redox manner are difficult to determine. However, certain trends are clear. Most trivalent alkyl phosphines will not metathesize with any pnictogen, but will react to give either an adduct or redox products. Alkylarsines will either metathesize or yield an adduct, but will only rarely pass into the pentavalent state. Antimony generally metathesizes with other antimony compounds if there is at least one good pair of bridging ligands (Cl or Br). Finally, bismuth compounds generally metathesize, however, trivalent bismuth compounds generally oxidize most other pnictogens.

Conclusion. Metathetical reactions provide the synthetic chemist with a large number of substituted trivalent pnictogens. The donor and acceptor properties of these compounds make them quite diverse in their chemical behavior and hence extremely valuable to the synthetic chemist.

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ORGANOTIN REAGENTS: VERSATILE INTERMEDIATES FOR ORGANIC SYNTHESIS

Reported by John Lloyd October 6, 1980

Organotin compounds have recently been shown to be versatile and useful reagents for organic synthesis.[1,2,3] Tin is a member of group IVa and may be expected to share many properties in common with carbon. Although the physical properties of many organotin compounds are very similar to the analogous carbon compounds, the reactivity of the tin-carbon bond is significantly different from that of the carbon-carbon bond.

An examination of some simple atomic properties of tin can give some insight into the reactivity of the tin-carbon bond. Electronegativity predicts the tin-carbon bond to be polarized but much less so than for other organometallic reagents such as organolithiums and Grignard reagents. Tin has a relatively large covalent radius so its reactions show little effect of steric factors. Also tin forms stronger bonds to halogens, oxygen and nitrogen than to carbon. However, caution must be used in predicting the reactivity of tin-carbon bonds from simple atomic properties alone. Other factors such as the polarizability of the tin-carbon bond and the ability to form higher co-ordination complexes lead to results which may have not been predicted on the basis of electronegativity and bond lengths and strengths alone.[1,2,3]

Organotin compounds can be synthesized by a number of methods, several of which are well adapted for laboratory synthesis. Transmetallation, in which nucleophilic attack by an organometallic on tin effects an exchange of ligands has been used to synthesize tetraorganotins 1, 2, 3, 4, 5, eq. (1).

$$R_3SnX + R'Li \longrightarrow R_3SnR' + LiX \qquad (1)$$

In the reverse sense, a triorganotin anion may react with an electrophile to produce a tetraorganotin, eq. (2).

$$R_3SnM + R'\text{-}X \longrightarrow R_3SnR' + MX \qquad (2)$$

$M = Li, Na, K$

Reagents such as trimethylstannyllithium will displace a halogen in alkyl and aryl halides,[6,7,8,9] add to the carbonyl of aldehydes and ketones,[10] and add to α,β-unsaturated carbonyl compounds[11,12,13,14,15] in both a 1,2 and 1,4 manner that can be controlled by the reaction conditions.[16] In hydrostannation reactions, trialkyltin hydrides add to carbon-carbon multiple bonds to produce the corresponding tetrasubstituted organotin.[17,18,19] If a leaving group is allylic to the multiple bond the organotin adds highly regiospecifically with allylic rearrangement.[20,21,22]

Due to the polarization of the tin-carbon bond, organotin compounds usually react with nucleophiles at tin and electrophiles at carbon. Transmetallation has been used extensively for cleavage of the tin-carbon bond and the synthesis of functionalized organolithiums.[4,9,10,23,24] A particularly attractive synthesis of functionalized vinyllithium reagents can be effected by a sequence of hydrostannation of an acetylene then transmetallation to form the vinyllithium reagent.[18,19,25,26]

The reactions of organotin compounds with electrophiles are some of the most interesting and useful reactions of organotins. Most of these reactions involve the reaction of an allyltin reagent at the gamma carbon with an electrophile. Catalysis by Lewis acid is usually employed in additions to carbonyl compounds[27,28,29,30,31] or a palladium catalyst in additions to alkyl halides.[5,33,34,35,36,37,38] The reaction of an organotin at the alpha carbon with an α,β-unsaturated ketone with titanium tetrachloride catalysis has recently been reported.[32] There have also been reports of transfer of organic groups to aryl chlorides.[33,34,35]

Other reactions which further illustrate the versatility of organotin reagents are those of functionalized organotins where the reaction does not involve the cleavage of the tin-carbon bond. Tin has been used as a protecting group for α,β-unsaturated ketones,[15] glycosides[42] and diols.[43] Organotin functionality may be accomodated on Wittig reagents,[23,44,45] organolithium reagents,[46,47] carbenes,[48] organoboranes[49] and in Diels-Alder reactions.[50] The products of these reactions may go on to participate in reactions of the tin-carbon bond as previously discussed.

It can be seen that organotin compounds are versatile reagents for organic synthesis. The key to their versatility lies in the intermediate reactivity of the tin-carbon bond. They undergo synthetically useful transformations involving cleavage of the tin-carbon bond yet the tin-carbon bond is compatible with a wide variety of functionality in the molecule. Organotin compounds are likely to become an even more powerful tool for the organic chemist in the future.

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OZONATIONS ON SOLID SUPPORTS

Reported by Joan Z. Suits October 9, 1980

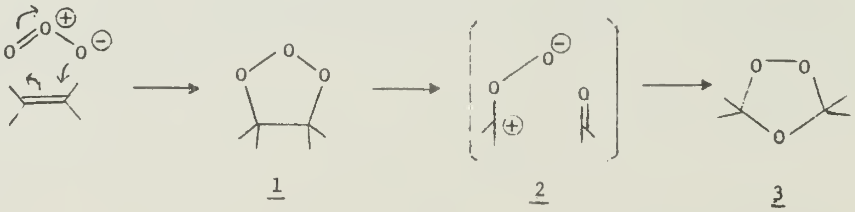
Introduction. Ozone is a versatile chemical reagent which has found much use, both in and out of the laboratory. Naturally occurring ozone in the stratosphere protects life from harmful energy from outer space; ozone has been used in the treatment of wastewater[1] and has been suggested as a possible deterrent to cancer cell growth.[2] Chemists use ozone to accomplish a variety of synthetic transformations, including cleavage of saturated and unsaturated carbon systems with introduction of an oxygen function and oxidation of functional groups.[3] In general, these reactions are performed in solution. Thus, it often happens that a solvent molecule will interfere in the ozonolysis process, resulting in the formation of various by-products.

Recent years have seen a development in the technique of performing reactions on a solid support, such as silica or alumina.[4] This technique has been applied to a number of reactions, including oxidations, reductions, and aliphatic and aromatic substitutions.[4] Recently, it has been used in a variety of ozonation reactions.[5] In general, a substrate is adsorbed onto silica gel and the mixture then cooled to -78°. Ozone is passed over the mixture and then, after removal of unreacted ozone, the mixture warmed to room temperature and the products isolated. This report will review ozonations on solid supports and attempt to illustrate advantages and disadvantages of the technique.

Olefins. The degradation of olefins by ozone to give carbonyl-containing compounds is by far the most familiar ozonolysis reaction. Additionally, it is an extremely complex reaction whose course depends upon solvent, temperature, and substituents on the double bond. The complexities of this reaction have been recently reviewed.[6]

In most systems, ozone adds as a 1,3-dipole to a carbon-carbon double bond, giving an initial molozonide 1 which decomposes to the "Criegee intermediate" 2, which then forms the ozonide 3 (Scheme I).

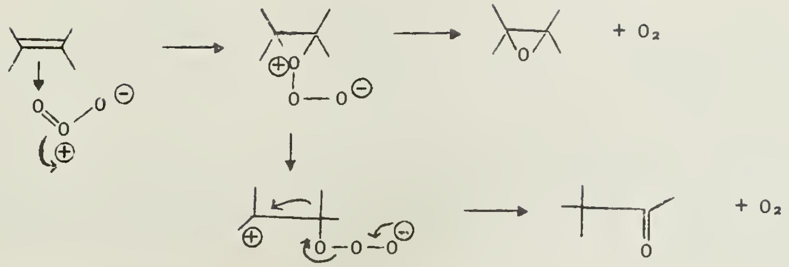
Scheme I



The ozonide 3 can then be treated with water, triphenyl phosphine, pyridine, or some other reducing agent to give the desired products.

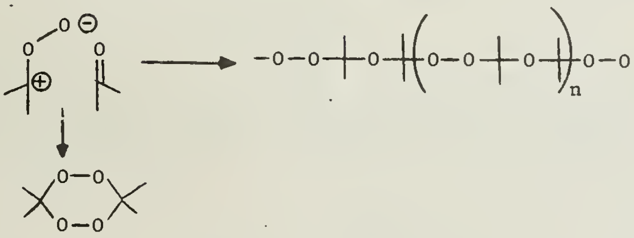
Even without direct interference by solvent molecules, formation of 3 does not occur without complication. If the substituents on the olefin are large, 1,3-addition may be blocked, resulting in electrophilic attack by ozone to give a peroxyepoxide which can form an epoxide or rearrange to form a carbonyl compound (Scheme II).

Scheme II



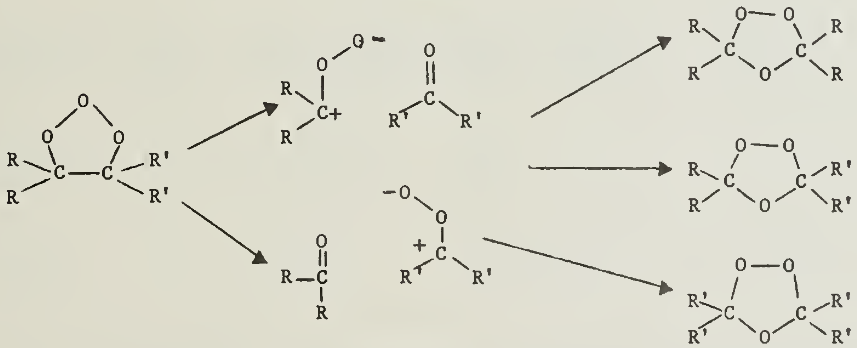
Additionally, the carbonyl oxide of 2 can react with itself to form dimers, or 2 can polymerise to peroxides (Scheme III).

Scheme III



Finally, fragmentation of 1 can occur in either (or both) of two directions. With unsymmetrically substituted olefins, this may result in formation of "crossed ozonides" (Scheme IV).

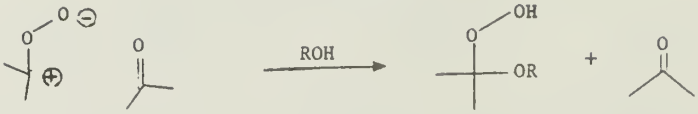
Scheme IV



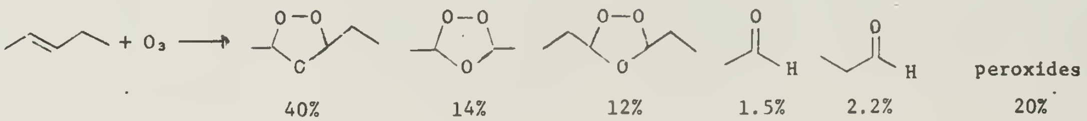
The formation of crossed ozonides is increased as the polarity of the solvent is increased.[7]

When alkenes are ozonized in aprotic solvents, the products isolated include monomeric ozonides, polymeric peroxides, and polymeric ozonides.[5,6] When the reaction is done in participating, protic solvents, yields of crossed ozonides increase and α-oxyalkylhydro peroxides are formed (Scheme V).

Scheme V



An example of problems in solution ozonolysis is given by the reaction of 2-pentene at -70° with ozone, which resulted in formation of both crossed ozonides as well as the normal ozonide, acetaldehyde, propionaldehyde, and peroxides, eq. 1.[8]

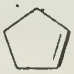
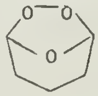
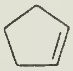
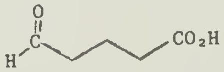
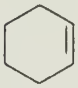
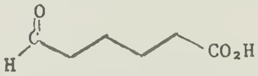
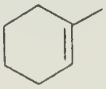
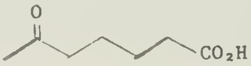
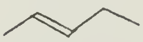
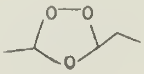


(1)

(relative yields)

In contrast, the ozonolysis of alkenes on a solid support results in formation of pure ozonides in high yield.[5] The results are summarized in Table 1.

Table 1

alkene	conditions	product	yield
	SiO_2, anh.		>80%
	SiO_2, 5% H_2O		>80%
	SiO_2, 5% H_2O		>80%
	SiO_2, 5% H_2O		>80%
	SiO_2, anh.		>90%

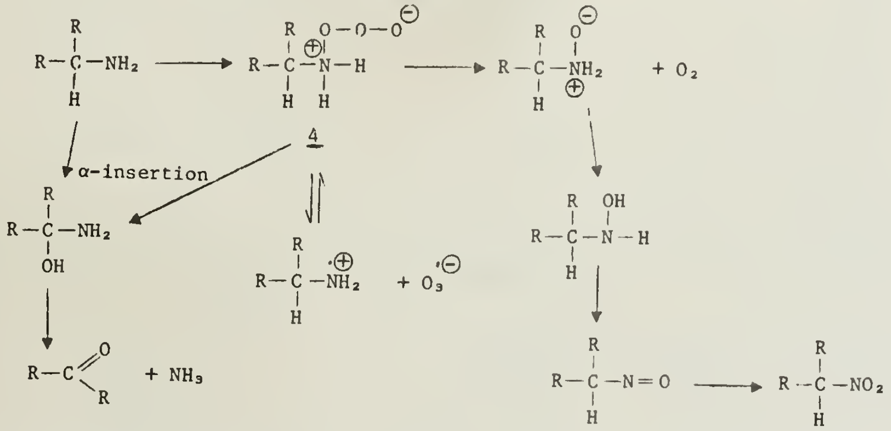
The reactions were performed by adding the alkene (1% by weight) to stirred silica gel at room temperature, cooling the mixture to -78°C, and blowing a stream of 3% O_3/O_2 over the mixture until it had a pale blue color. After removal of unreacted ozone and warming to room temperature, the product was eluted with methylene chloride.

Under anhydrous conditions, pure ozonides can be isolated, which can then be treated with reducing agents to give desired products. If the reaction is done in hydrated silica gel, the products obtained are those (ideally) expected from an aqueous work-up, without side reactions by solvent.

Presumably, the mechanism for the reaction is the same as in solution.[6] Thus, the problem with bulky substituents on olefins (Scheme II) might still be expected to cause reactions other than that of 1,3-dipolar addition.

Amines. Ozone has long been used to oxidize amines to the corresponding nitro compounds.[9] The mechanism by which oxidation occurs is initial electrophilic attack by ozone on the amine nitrogen to give a zwitterion intermediate (4), which loses oxygen to give a nitroxide. The nitroxide is then oxidized to the nitroalkane. Other possibilities in the reaction include reversible decomposition of 4 to a zwitterion diradical, and insertion of ozone into the α-CH bond resulting in formation of a ketone. These reactions are shown in Scheme VI.

Scheme VI



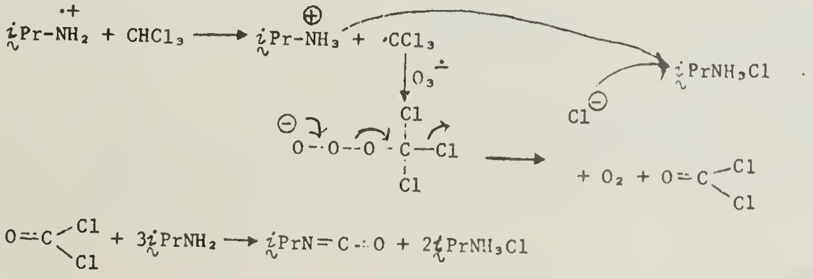
When amines are ozonized in solution, considerable side reactions can occur. An example is the ozonation of isopropyl amine.[10] The results are illustrated in Table 2.

Table 2. Ozonation of Isopropyl Amine

		Products--% Yield			
Solvent	Temp. (°C)	2-nitropropane	acetone	isopropyl-isocyanate	isopropyl ammonium chloride
$CHCl_3$	-65	25-28	4-6	15-18	48-51
$CHCL_3$	-30	22-23	10	5	40-47
$CHCl_3$	0	14-15	19-22	5	42-46
CH_2Cl_2	-78	36	12	5	43
pentane	-78	53	8	0	0

Acetone is formed by α-insertion. The formation of isopropylammonium chloride and isopropyl isocyanate results from interception of 4 by solvent (Scheme VII).

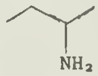
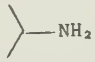
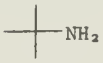
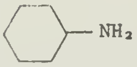
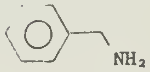
Scheme VII



Similar results are obtained for n-butylamine[10] and t-butylamine.[11]

In contrast, ozonation of amines on silica gel results primarily in formation of the corresponding nitro product in high yield, with some formation of carbonyl product.[12] The results are shown in Table 3.

Table 3. Ozonation of Amines on Silica Gel[12]

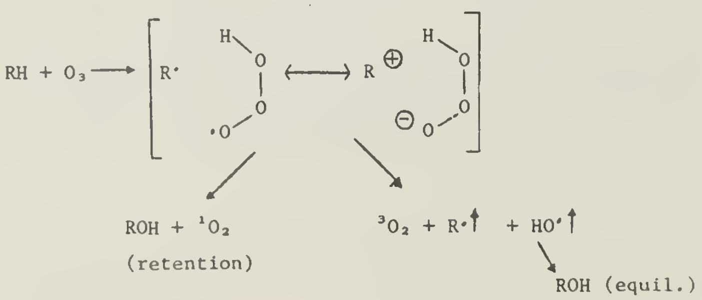
	products-% yield	
amine	nitro compound	carbonyl derivative
	70	2
	65	5
	70	none
	69	4
	66	6

It was found[12] that the yield of nitro product decreased as the ratio of amine/silica gel, temperature, or water content of the silica gel was increased. The dependence of yield on the amine/silica gel ratio was postulated to be the result of interactions between intermediates in the amine ozonolysis and unreacted amine. Similarly, water in the silica would act as a nucleophilic, protic solvent would act, decreasing yield.

Alkanes. It is thought by some scientists that oxidation of alkanes by ozone contributes to air pollution.[13] Compared to other organic compounds, alkanes react slowly with ozone, forming alcohols which in some cases are further oxidized to ketones.[13,14] Generally, a carbon-hydrogen bond is cleaved (the order of reactivity is 3°>2°>1° with a ratio of 100:10:1) but carbon-carbon bonds have also been cleaved.[15]

The mechanism by which alkanes are oxidized by ozone in solution is not known. It has been postulated that initial hydrogen abstraction results in formation of an intermediate which has both radical and ionic character.[14] This intermediate can then decompose via a radical mechanism, resulting in an alcohol with retention or inversion of configuration (Scheme VIII).

Scheme VIII



It has been found that although solvent polarity does not greatly influence the configuration of alcohols resulting from the ozonation of cis-1,2-dimethylcyclohexane (Table 4), it does influence the extent to which the alcohol formed from cyclohexane are further oxidized to ketones (Table 5).[14a]

Table 4. Alcohols from cis-1,2-Dimethylcyclohexane [14a,b]

solvent	relative % yields cis-alcohol	trans-alcohol
cis-1,2-dimethylcyclohexane (DMC)	85	15
cis-1,2-DMC - acetic acid	85-90	15-10
cis-1,2-DMC - $C_{18}H_{38}$	91	9
cis-1,2-DMC - acetone	65	35
cis-1,2-DMC - ethyl acetate	78	22
cis, 1,2-DMC - chloroform	85	15

Overall, the reaction proceeds with 60-70% retention of configuration.[14b]

Table 5. Ozonation of Cyclohexane

solvent	relative % yields alcohol	ketone
cyclohexane	79	21
cyclohexane-acetone	33	67
cyclohexane-ethyl acetate	40	60
cyclohexane-diphenylamine	69	31

Other products which have been isolated from cyclohexane ozonation include peroxides and adipic acid, formed by carbon-carbon σ bond cleavage.[15] Oxidation of the alcohol to the ketone presumably proceeds via electrophilic ozone attack on oxygen, similar to the attack of ozone on amines.[9] In superacid media, the mechanism of the initial attack is presumed to proceed via a protonated ozone insertion into the alkane σ bond, but this does not significantly change the outcome.[16]

The technique of dry ozonation was originally developed for use with alkanes.[17] It was found that on silica gel at -78° an almost quantitative conversion of alkane to alcohol, almost exclusively with retained configuration, resulted. Ketones were also observed but this reaction did not occur as readily as in solution. These results are summarized in Table 6.

In contrast to the formation of alcohols in solution, which proceeds with 60-70% stereospecificity,[14] formation of alcohols on solid support proceeds with 78-99% stereospecificity.[17]

Oxidation by ozone of alkanes can also result in carbon-carbon bond cleavage, especially at higher temperatures.[18] As an example, the results from the ozonation of 3-methylpentane are shown in Table 7.

3-Methyl-2-pentanone is formed from the alcohol, which would be expected to oxidize under the reaction conditions. Presumably, both carbon-carbon and carbon-hydrogen cleavage occur via insertion of ozone into the respective σ bonds (Scheme IX).[18]

Table 6. Ozonation of Alkanes[17a]

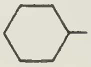
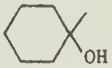
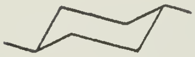
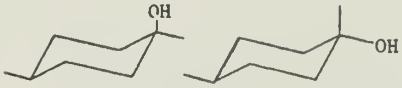
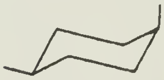
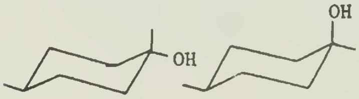
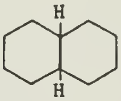
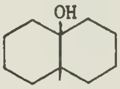
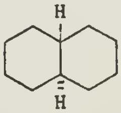
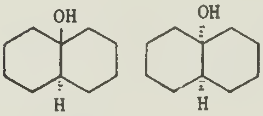
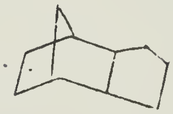
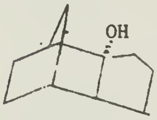
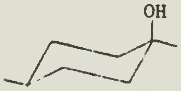
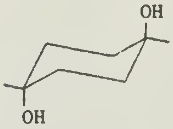
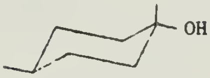
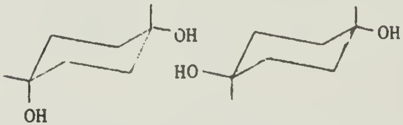
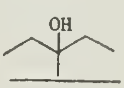
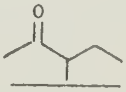
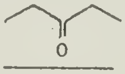
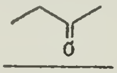
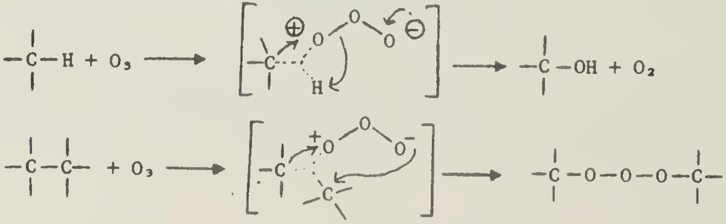
substrate	products	% yield(s)	conversion
		65	>99.5
		79, 0.6	80
		76, 3.5	92
		99	>99.5
		72, 10	88
		90	>99.5
		95	>99.5
		76, 5	97

Table 7. Ozonation of 3-Methylpentane[17]

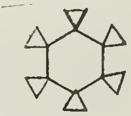
temp (°C)				
-45	32	15	20	33
-23	30	15	20	35
0	22	13	20	44
30	8	10	23	60

Scheme IX



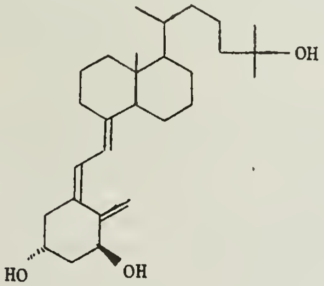
The trioxide formed by carbon-carbon insertion decomposes to give products. Such an intermediate has also been postulated in the dry ozonation of bicyclo[n.1.0.]alkanes.[19]

The selective hydroxylation of aliphatic compounds by means of ozone insertion into the carbon-hydrogen bond has in contrast found much more use, in the syntheses of unusual molecules such as [6]-rotane[21] and in many natural products syntheses.[22-27]



[6]-rotane

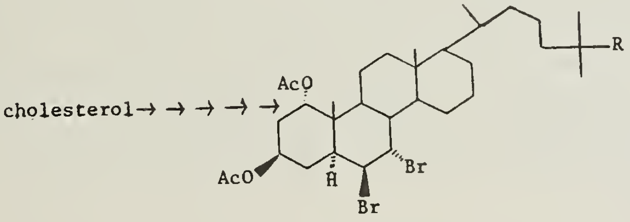
An example of this is the synthesis of 1-α,25-hydroxy vitamin D_3(4).[24a]



4

The key to the synthesis was the regioselective hydroxylation at C-25 of the tetrasubstituted cholestane derivative 5a, which was synthesized in five steps from cholesterol (Scheme X).

Scheme X

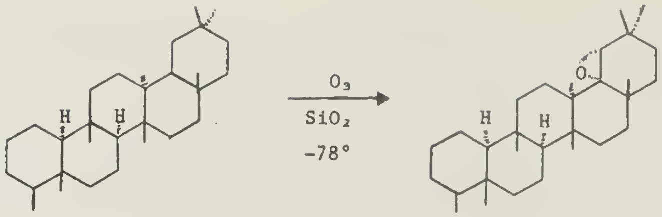


a. R=H
b. R=OH

5

5a was adsorbed onto silica gel, cooled to -78°, the mixture saturated with ozone, and then slowly warmed to room temperature. This cooling/saturation/warming procedure was repeated five times and the mixture eluted with ethyl acetate to give 5b, which was transformed in three steps to 4 in good overall yield.[24a] Similar results have been obtained with other steroid derivatives.[24b]

Recently, similar conversions have been attempted with triterpene derivatives.[25,26] Thus, friedelane (6) was converted into 18β-19β-epoxyfriedelane (7) in 48% relative yield.[25]



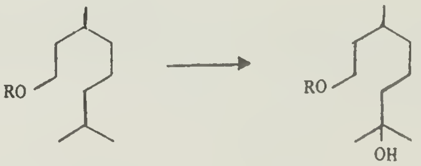
6 7

Other products isolated included 19-oxo- and 16-oxofriedelane and friedelin.[25] The regioselectivity of the triterpene and steroid conversions is postulated to result from preferential adsorption of the A-ring moiety onto the silica gel for steric reasons, leaving the rest of the molecule available for reaction with ozone.[24,25]

Comparison of Solution and Dry Ozonations--Conclusion. Results so far indicate that ozonations in dry media avoid many of the complications arising from the solvated reactions; most of the side reactions which do occur seem to result from the chemistry of the ozone-substrate reaction itself.

The disadvantages of dry ozonation relative to solution ozonation are that in general it is difficult to monitor the course of the reaction; yields of products, while good, tend to be erratic; and there are technical limitations to the scale which can be used.[26] An interesting method to circumvent these problems has been recently proposed by Beckwith.[26] The problem was regioselective hydroxylation by ozone of the 7-position of 3,7-dimethyloctanol derivatives, equation 2.[22,26]

R=H, Ac



(2)

In ethyl acetate solution, the yield of the desired product was less than 35%; on silica gel, the yield was increased to 65%.[22] To further improve the yield, the substrate was first adsorbed onto silica gel and the mixture suspended in Freon-11. Ozone was bubbled into the mixture, and upon workup, over 92% of the desired compound was isolated.[26] This combination of the best of both techniques may well prove to be the most useful technique possible.

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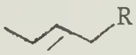
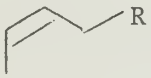
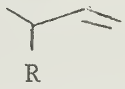
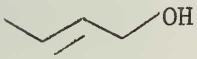
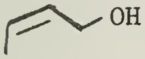
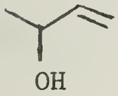
BIS(TRIPHENYLPHOSPHINE)NICKEL DICHLORIDE CATALYZED GRIGNARD SUBSTITUTION REACTIONS

Reported by Steve Ashburn October 13, 1980

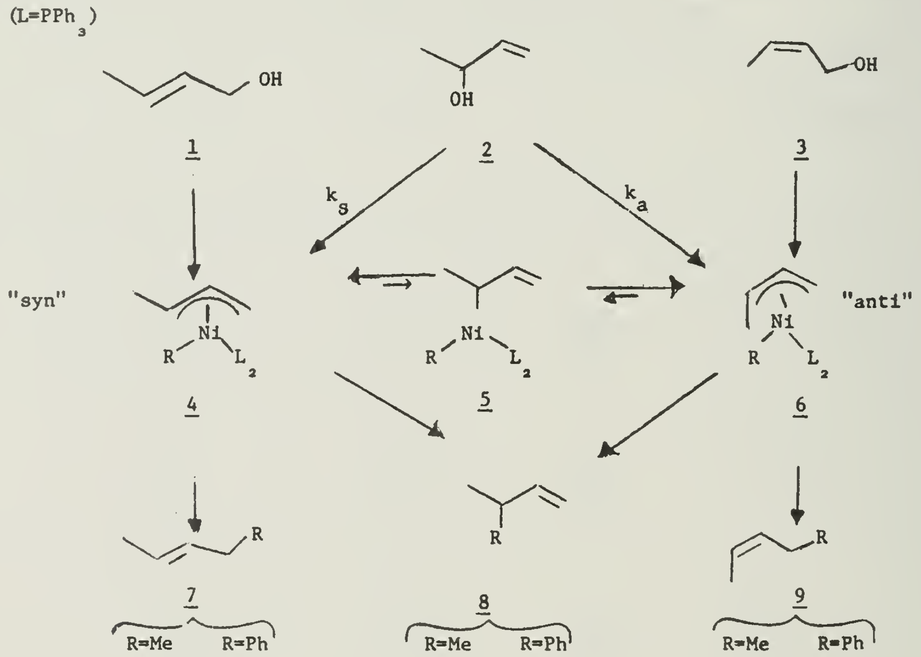
The reaction between Grignard reagents and allyl alchohols in the presence of catalytic amounts of phosphine-ligated nickel dichloride--the Felkin reaction--leads to replacement of the hydroxy group by hydrogen or an alkyl function, depending on the nature of the organometallic reagents.[1] Grignard reagents containing β hydrogens lead to hydrogenolysis, while Grignard reagents having no β hydrogens yield alkylated or arylated products. Thus, for example, reaction of three butenols with propylmagnesium bromide under the influence of the nickel catalyst yielded the hydrogenated butenes,[1f] whereas exposure of the same butenols to methyl and phenylmagnesium bromide afforded substituted olefins[1d] (Table 1).

Table 1. Yields and proportions of olefins obtained from the action of Grignard reagents RMgBr (R=Me, Ph, Pr) upon cis- and trans-2-butenol and α-methylallyl alchohol in the presence of $(\emptyset_3P)_2NiCl_2$

Alchohol	R	% Yield			
	H	90	84	3	13
	Me	87	54	0	46
	Ph	73	65	1	34
	H	80	31	39	30
	Me	80	7	2	90
	Ph	64	7	35	59
	H	61	53	28	19
	Me	82	29	2	69
	Ph	31	40	16	44

The latter reactions are outlined in Scheme I.[1c] The proposed system involves two stereoisomeric π-allylnickel intermediates 4 and 6.[2] Alchohols 1 and 3 are expected to lead first to the "syn" and "anti" complexes 4 and 6, respectively. Alchohol 2, however, can lead to both 4 and 6, which must then afford the same mixture of olefins as are formed from 1 and 3, respectively. If these reactions occur exclusively via the π-crotyl intermediates 4 and 6, then the proportions of olefins formed from α-methylallyl alchohol 2 must correspond to exactly the same weighted average of the proportions of the same olefins formed from the cis and trans alchohols 1 and 3, the common weighting factor being the rate ratio k_s/k_a[3]. The proportions of olefins obtained from the three isomeric butenols (1, 2 and 3) and two Grignard reagents (MeMgBr and PhMgBr) are shown in Scheme I, together with the weighting factors (k_s/k_a)[4] calculated from them. It is apparent that these weighting factors are indeed identical within experimental error, for all the olefins (7, 8 and 9), which strongly indicates that the reactions take place via π-allylnickel intermediates as shown.[1c] Catalytic cycles for both nickel-induced substitution and hydrogenation have been proposed.[1c,d,f]

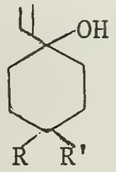
Scheme I.[1c] Postulated stereoisomeric π-crotylnickel intermediates in the butenol system, with the percentage proportion of olefins (7, 8 and 9, R=Me and Ph) formed in the reactions of the butenols 1, 2 and 3 with MeMgBr and PhMgBr (catalyzed by $(\emptyset_3P)_2NiCl_2$), and the calculated values of the rate ratio k_s/k_a[4].



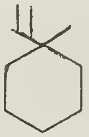
		7 R=Me	7 R=Ph	8 R=Me	8 R=Ph	9 R=Me	9 R=Ph
Percentage proportion of olefin formed	from 1	54.0	65.5	46.0	34.0	0	0.5
	from 2	29.4	39.7	68.8	44.1	1.8	16.2
	from 3	7.4	6.6	90.2	58.6	2.4	34.8
k_s/k_a calc.[4]		0.90	1.3	0.94	1.4	(-)[5]	1.2

The utility of the Felkin reaction has been extended to the synthesis of structurally complex diterpenes as the following study by Wenkert indicates.[6]

Treatment of 1-vinylcyclohexanol (10a) with methylmagnesium bromide in the presence of the nickel catalyst affords a greater than 3:1 mixture of 1-methyl-1-vinylcyclohexane (11) and n-propylidenecyclohexane (12a).



10a, R=R'=H
b, R=t-Bu, R'=H
c, R=H, R'=t-Bu



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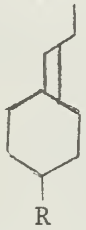
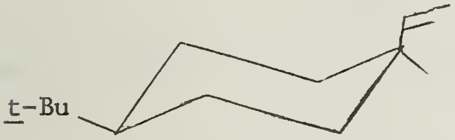


12a, R=H
b, R=t-Bu

As the construction of methylated, vinyl-substituted quaternary carbon sites was of possible importance in terpene synthesis, a determination of the stereochemical consequence of the alkylation reaction was necessary and was made in the following fashion.[6] Exposure of the stereoisomeric alchohols 10b and 10c to methylmagnesium bromide and the nickel catalyst produced the terminal olefins 13 and 14 and the trisubstituted olefin 3b in a 77:4:19 ratio from either alchohol.



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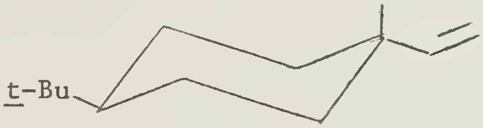
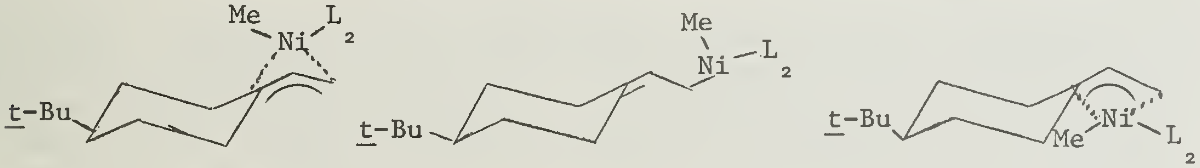


14

The observed high stereoselectivity may result from the equilibrium between π- and σ-allylnickel complexes (15a $\rightleftarrows$ 15b $\rightleftarrows$ 15c) favoring the least sterically encumbered, quasi-equitorial π-allylnickel intermediate 15c.



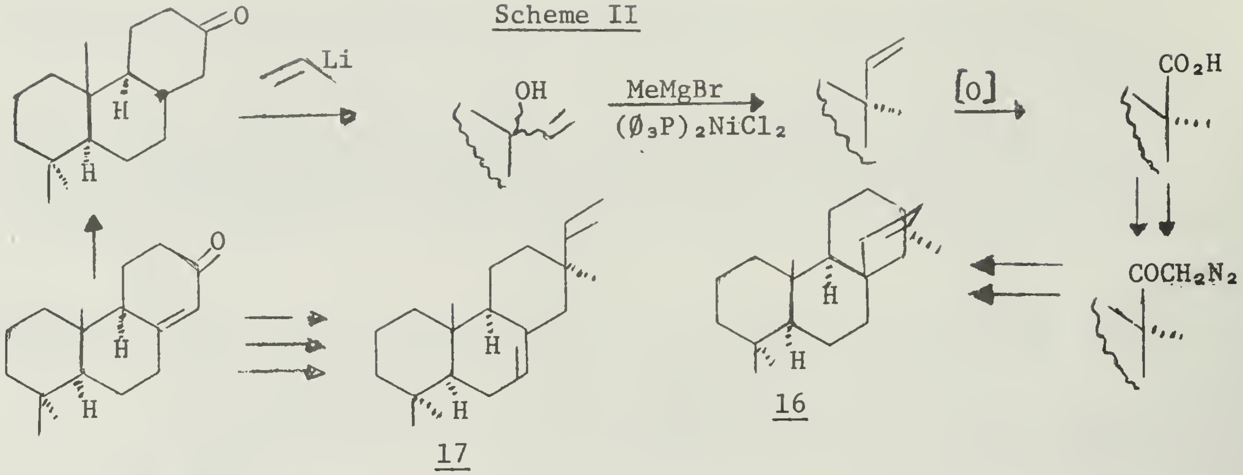
a b c

15

Since vinylcarbinols are easily prepared from aldehydes or ketones and the nickel-induced methylation process shows high preference for quaternization over terminal carbon alkylation, and is furthermore greatly stereoselective, a facile conversion of keto groups into methyl vinyl quaternary chiral centers has become available.

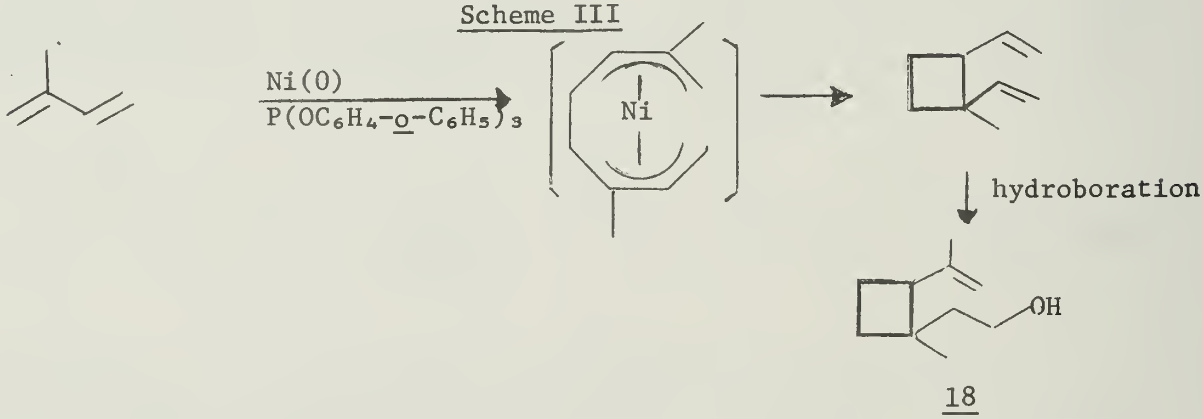
The above two-step conversion was utilized in the partial synthesis of several diterpenes which have methyl vinyl sites as common features, e.g., hibaene (16) and hydrocarbon 17, which interestingly enough, is the only one of the four possible pimaradienes which have not yet been found in nature (Scheme II).[6]

Scheme II



Interestingly, π-allylnickel(0) coupling has also been used in a two-step synthesis of another biologically important natural product, grandisol (18), a component of the sex pheromone of the male boll weevil (Scheme III).^{7,8}

Scheme III

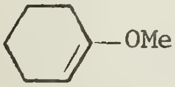
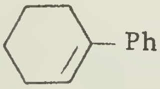
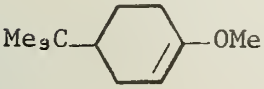
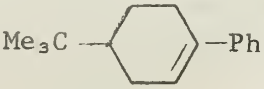
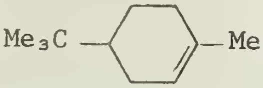
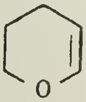
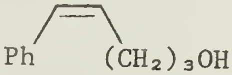
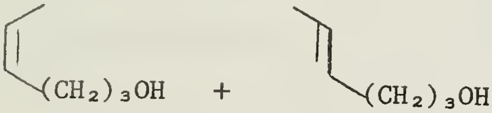
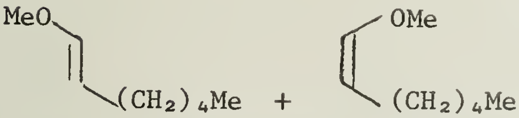
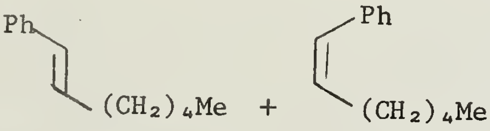
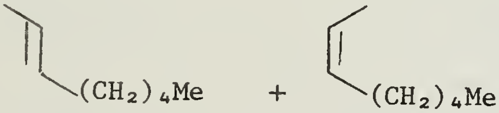
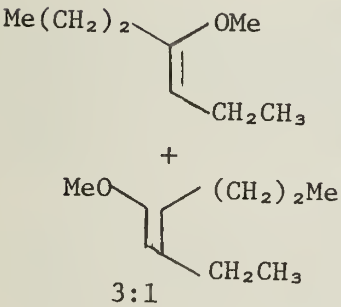
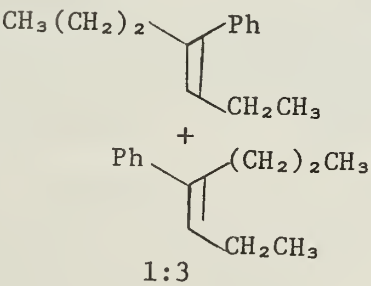
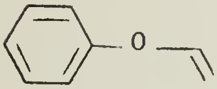
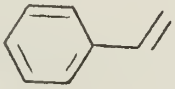
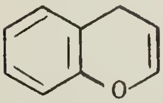
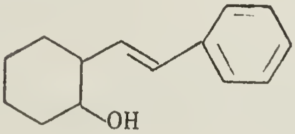
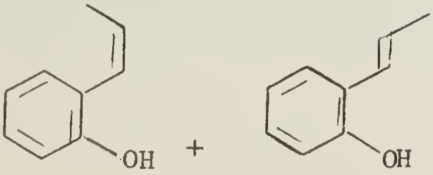


In further investigations, a new reaction was encountered: the direct substitution of alkoxy groups bound to carbon-carbon double bonds by alkyl and aryl functions.^{9} Enol ethers are attacked by phenyl and methyl Grignard reagents in the presence of the nickel catalyst to produce olefins, and nickel-mediated arylation of aryl ethers affords biaryls, as can be seen in Tables 2 and 3.

In a mixture of *cis* and *trans*-4-methoxy-3-heptene (keto enol ether), substitution by phenylmagnesium bromide occurs such that a predominantly *trans* mixture is converted to a predominantly *cis* mixture, a greatly different result than with the *cis*- and *trans*-1-methoxy-1-heptene mixture (aldehyde enol ether) (Table 2).

Highly substituted enol ethers, enamines and enolates do not undergo nickel-induced reaction with phenylmagnesium bromide (Scheme IV).

Table 2. The Reactions of Enol Ethers with Phenylmagnesium and Methylmagnesium Bromides [9]

Ether	Olefinic Products	% Yield
		71
		75
		59
		64
		74
 1.3:1	 1.7:1	79
	 1.4:1	66
 3:1	 1:3	86
		93
		61
	 4:1	75

Scheme IV[9]

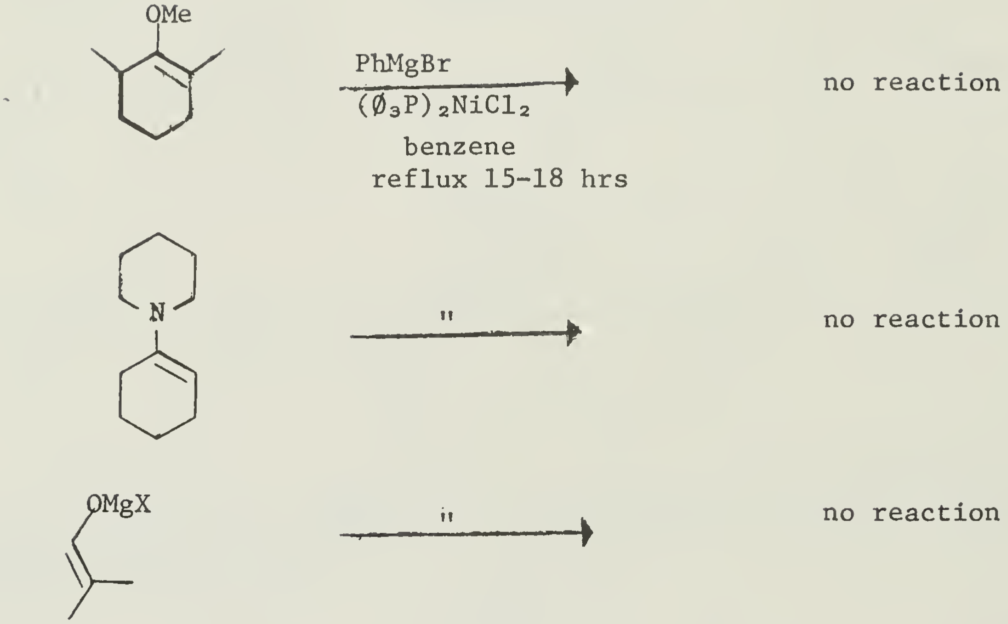

OMe
PhMgBr
$(Ø_3P)_2NiCl_2$
benzene
reflux 15-18 hrs
no reaction
N
"
no reaction
OMgX
"
no reaction

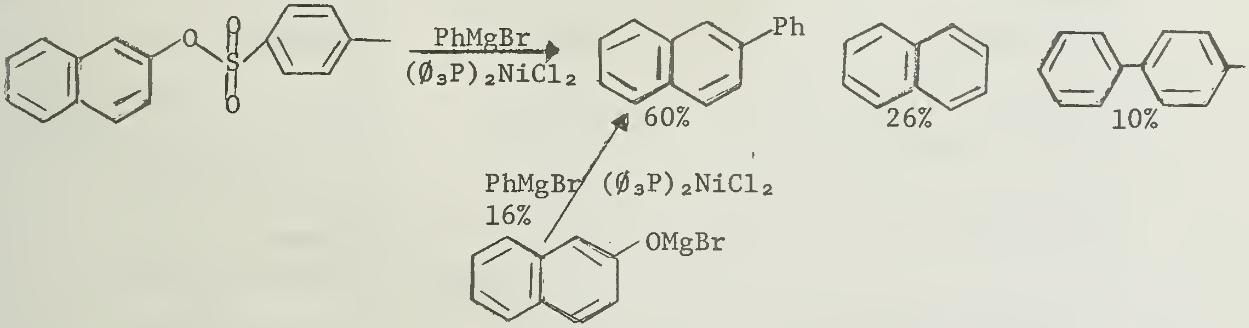
Table 3. The Reactions of Aryl Ethers with Phenylmagnesium Bromide[a,9]

Ether	Products	% Yield
1-methoxynaphthalene	1-phenylnaphthalene	70
2-methoxynaphthalene	2-phenylnaphthalene	77
2,3-dimethoxynaphthalene	2,3-diphenylnaphthalene	45
m-dimethoxynaphthalene	*m*-methoxybiphenyl	23 (79)
p-dimethoxybenzene	*p*-methoxybiphenyl,	33 (37)
	p-terphenyl	24 (27)
p-methoxybiphenyl	*p*-terphenyl	30 (55)
m-cresyl methyl ether	*m*-methylbiphenyl	16 (74)
p-cresyl methyl ether	*p*-methylbiphenyl	20 (60)

[a] Isolated product yields are based upon the initial ether quantity, whereas those in parentheses take into account recovered ether.

In contrast to the inertness of methoxybenzene toward phenylmagnesium bromide, 1- and 2-methoxynaphthalene undergo ready substitution in the presence of the nickel catalyst, and even a vicinal dimethoxynaphthalene undergoes facile interaction with the organometallic reagents, in the face of the inertness of *o*-dimethoxybenzene and *o*-cresyl methyl ether under these conditions. Substitution on the naphthalene nucleus occurs even with β-naphthyl *p*-toluenesulfonate and magnesium β-naphthoxide (Scheme V)[10] in 60% and 16% yield, respectively, in addition to side products.

Scheme V



Recent studies of the reactions of the analogous sulfur compounds have shown that alkenyl sulfides, benzene-thiols and aryl sulfides undergo nickel-mediated conversion to the corresponding substituted olefins (primarily with retention of configuration), toluenes and biphenyls in medium to high yields, as revealed by Tables 4 and 5.[11,12]

In general, the sulfur compounds undergo the catalyzed Grignard reaction more readily than the corresponding oxy compounds.[11] For example, the facile interaction of aryl sulfides with MeMgBr and the nickel catalyst as well as the ready substitution of aromatic sulfhydryl groups by PhMgBr provide a remarkable contrast to the inertness of anisoles and phenolic hydroxy groups toward these reagents, respectively.[9]

In contrast to the observation of both alkylation and reduction products in the nickel-mediated reaction of organomagnesium reagents having labile β hydrogens with enol ethers,[9] no reduction product resulted from the reaction of the latter reagents with thio enol ethers and aryl sulfides[11,12] (cf. Table 5).

Selenium compounds are also transformed into substituted olefins and aryls in analogy to the preceding sulfur cases.[11] Thus, the nickel-catalyzed reaction of phenyl vinyl selenide with *p*-tolylmagnesium bromide yielded *p*-methylbiphenyl (60%) and *p*-methylstyrene (25%).[11]

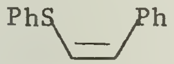
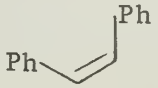
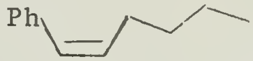
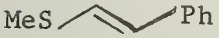
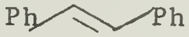
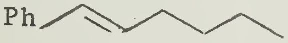
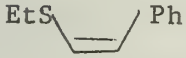
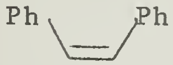
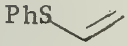
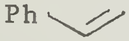
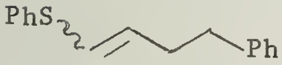
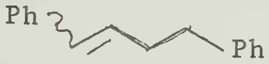
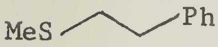
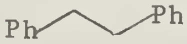
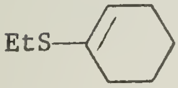
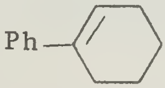
In view of the ease of preparation of enol ethers and alkenyl sulfides[13] from aldehydes and ketones, a facile two-step procedure for the conversion of keto groups into, inter alia, trisubstituted olefins has become available. In addition, keto groups may be converted with high stereoselectivity to methyl vinyl quaternary carbon centers *via* nickel-induced methylation of the keto-derived vinylcarbinols. Aryl sulfur compounds are remarkably reactive toward nickel-catalyzed substitution; thus, it is observed (vide infra) that aryl sulfides, aryl thiols, aryl sulfoxides, aryl sulfones,

Table 4. The reactions of thioenol ethers and benzenethiol derivatives with methyl, phenyl and p-tolylmagnesium bromides [11]

Thio compound	RMgX	Products	% Yield
1-Methylthio-oct-1-ene (4:1)[a]	MeMgBr	Non-2-ene (5:1)	71
	PhMgBr	1-Phenyloct-1-ene (4:1)	80
Thiophene	PhMgBr	1,4-Diphenylbuta-1,3-diene	85
Thianaphthene	MeMgBr	o-Propenyltoluene (1:3)	48
	PhMgBr	o-Phenylstilbene (1:1)	61
Dibenzothiophene	MeMgBr	o,o'-Dimethylbiphenyl	73
	PhMgBr	o,o'-Quaterphenyl	52
Benzenethiol	MeMgBr	Toluene	64
	p-tolylMgBr	p-Methylbiphenyl	62
p-t-Butylbenzenethiol	MeMgBr	p-t-Butyltoluene	50
	PhMgBr	p-t-Butylbiphenyl	30
Thioanisole	MeMgBr	Toluene	97
	p-tolylMgBr	p-Methylbiphenyl	74
p-t-Butylthioanisole	MeMgBr	p-t-Butyltoluene	55
	PhMgBr	p-t-Butylbiphenyl	53
Diphenyl sulfide	MeMgBr	Toluene	74
	p-tolylMgBr	p-Methylbiphenyl	74
p-t-Butylthioanisole oxide	MeMgBr	p-t-Butyltoluene	50
Diphenyl sulfoxide	MeMgBr	Toluene	77
	p-tolylMgBr	p-Methylbiphenyl	57
Methyl phenyl sulfone	MeMgBr	Toluene	97
	p-tolylMgBr	p-Methylbiphenyl	45
Diphenyl sulfone	MeMgBr	Toluene	70
	p-tolylMgBr	p-Methylbiphenyl	53
Sodium p-toluenesulfinate	p-tolylMgBr	p-Methylbiphenyl	27

[a] trans:cis Ratio

Table 5. The reactions of alkyl and aryl sulfides with phenyl- and butylmagnesium bromides [12]

Sulfide	RMgX	Product	% Yield	trans:cis
	PhMgBr		97	6:94
	BuMgBr		45	6:94
	PhMgBr		85	95:5
	BuMgBr		64	95:5
	PhMgBr		96	5:95
	PhMgBr		60	--
	PhMgBr		64(81)	mixture
PhSMe	BuMgBr	Ph-Bu	29	--
	PhMgBr		0	--
	PhMgBr		56	--

aryl sulfinates and aryl sulfonates are converted to the corresponding olefins, toluenes and biphenyls in medium to high yields.

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2. For further mechanistic details, see references 1c, d and f.
3. This must be true whether or not the isomeric π-crotyl complexes 4 and 6 are interconverted (e.g., via the σ-complex 5), and whatever the relative rate of this interconversion (if it occurs); slow (anti→syn) interconversion of π-crotylnickel complexes has been observed by C. A. Tolman, J. Am. Chem. Soc., 92, 6777 (1970).
4. k_s/k_a calc.$=(X_2-X_3)/(X_1-X_2)$ where X_n stands for the percentage proportion of any one olefin X (X=7, 8 or 9, R=Me or Ph) formed from the alcohol n (n=1, 2 or 3).
5. The proportions of cis-2-pentene (9, R=Me) formed are so close together that it is not possible to calculate a significant value of k_s/k_a for this olefin (see ref. 4).
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PERMUTATIONAL ISOMERIZATION IN HEXACOORDINATE DERIVATIVES OF NON-METALLIC ELEMENTS

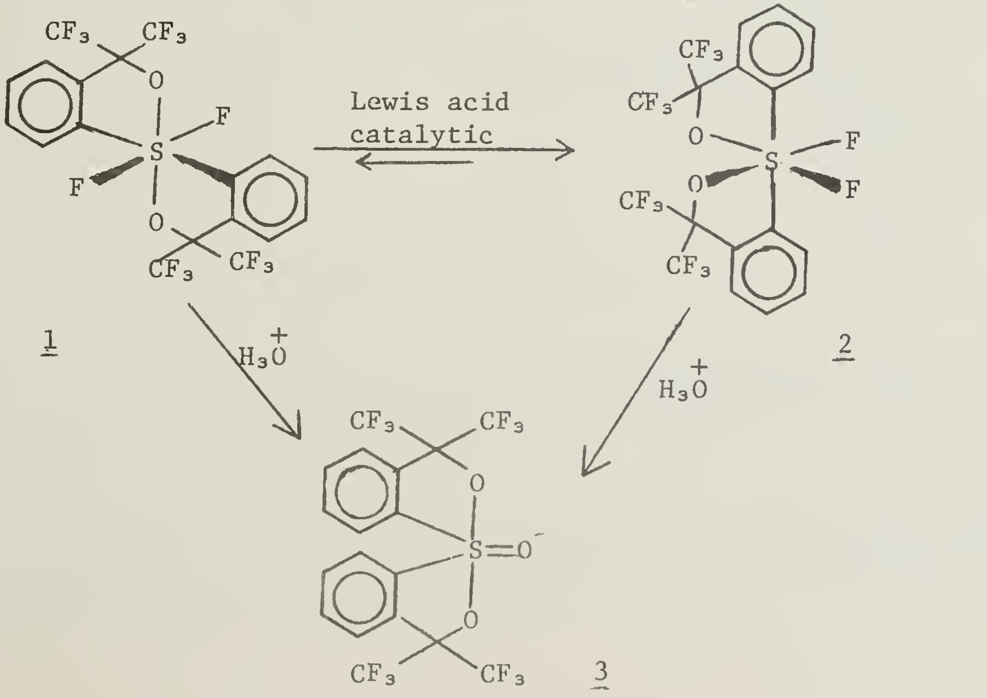
Reported by Ronald S. Michalak October 16, 1980

Hypervalent, or electron-rich bonding, is a term used to describe molecules formed by elements whose formal valence-electron shell contains electrons in excess of the traditional stable octet. Although molecules such as PCl_5 and $SeCl_4$ were prepared before 1820 by Davy and Berzelius, it has been only recently that the bonding in these molecules has been described.[1]

Although the seminar will focus on non-metal species, the majority of geometrical isomerizations which have been studied have been on compounds of the type ML_6, where M is a metal and the ligands are mono- or bidentate.[2] Isomerization mechanisms which involve no bond rupture at the central atom include the Bailar twist[3] (rotation about a C_3 axis) and the Ray and Dutt twist[4] (rotation about a C_2 axis). A dissociative mechanism can occur through tetra- or pentacoordinate intermediates.[2]

Few geometrical isomers of hexacoordinated non-metal species have been reported. The recently reported[5] isomerization of some hexacoordinate phosphorus anions showed the cis isomer to predominate in equilibrium at room temperature. The only chalcogen (S,Se,Te) for which cis and trans isomers of the same composition has been earlier reported is tellurium.[6]

Some cis hexacoordinate sulfur compounds (persulfuranes) are known. With the exception of a cis persulfurane reported by Cady,[7] all of these are constrained in a cis configuration by incorporation of the sulfur in a ring system.[8] We have isolated 1 and 2 and studied the acid catalyzed conversion of 1 to the more stable 2. Thermochemical studies of the hydrolysis of 1 and 2 to the common product 3 show 2 to be favored by 2.0 ± 0.5 kcal/mole over 1. The non-dissociative twist mechanisms for the conversion of 1 to 2 have activation barriers greater than 45 kcal/mole. This was determined by heating a solution of 1 in quinoline at 235°C for 18 h without any detectable isomerization.[9]



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SYNTHESIS AND UTILITY OF VINYLSILANES IN ORGANIC SYNTHESIS

Reported by Pam Albaugh-Robertson October 23, 1980

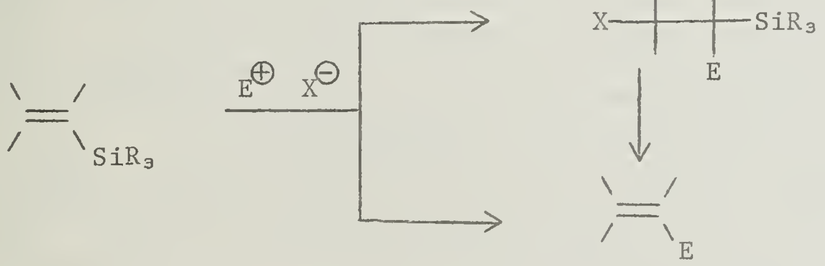
In the past decade a great deal of work has been reported on the use of silicon reagents, particularly in the area of synthetic organic chemistry.[1] The focus of this account is the synthesis and utility of organosilicon reagents in which silicon is ultimately bonded to four carbon atoms with at least one of these carbons possessing unsaturation, that is, vinylsilanes.

Silicon differs electronically from carbon in that it is more electropositive than carbon and has vacant d-orbitals. From these facts several trends are observed:[1,2] 1) a Si-C bond is more polarized than a corresponding C-C or C-H bond and thus is more susceptible to attack by oxygen or halogen nucleophiles; 2) the electron-releasing capability of silicon allows a Si-C bond to stabilize a β-carbonium ion;[3] 3) the electron-withdrawing capability of silicon allows it to stabilize an adjacent carbanion. These aforementioned properties are quite evident in the synthesis and reactions of vinylsilanes.

Vinylsilanes can be prepared from a variety of substrates, depending in part on the substitution needed in the vinylsilane. Typical substrates used include vinyl halides, acetylenes, ketones, and compounds already containing a Si-C bond. Vinyl halides can be coupled with a chlorosilane by treatment with sodium[4] or the vinyl halide may be metallated prior to reaction with a chlorosilane.[5] Acetylenes or the 1-silylacetylenes undergo hydrosilation,[6] hydroboration,[7] hydroalumination,[8] reduction,[6b] hydrogenation,[9] or reaction with copper reagents,[10] as well as many other reagents,[11] to yield vinylsilanes. Ketones can be converted to vinylsilanes by reaction with bis- or tris- (trimethylsilyl)-methyllithium[12] or by the reaction of the alkenyllithium derived from an arenesulfonylhydrazone with a chlorosilane.[13]

Vinylsilanes often exhibit high degrees of regio- and stereo-selectivity in reactions. Addition of electrophiles (see Scheme I) usually leads to overall electrophilic substitution via loss of the silyl group.[1,14,15,16,17]

Scheme I



The electrophile becomes bound to the carbon originally bearing the silicon atom, and the reaction may proceed with retention or inversion of geometrical configuration depending on the reaction conditions.

The Si-C bond is stable to free-radical reactions and cycloaddition reactions.[1] The vinylic Si-C bond is generally resistant to nucleophilic cleavage, with the notable exception by fluoride ion when there is a β-hydroxyl in the allylic position.[1,18] Certain organometallics can add to vinylsilanes if there is a leaving group in an allylic position, no substitution on the vinylsilane, or if there is an additional anion-stabilizing group on the α-carbon.[1,19,23] Addition across the double bond,[20,15,17] for example, hydroboration,[21] also occurs without cleavage of the C-Si bond.

Epoxidation of vinylsilanes leads to the epoxysilanes which can be transformed to carbonyl compounds or other epoxides.[22] The presence of a halogen on the double bond of a vinylsilane allows for further substitution of the double bond.[23]

Vinylsilanes can be valuable intermediates for stereocontrolled syntheses. But, the employment of vinylsilanes in organic synthesis has only begun. Therefore, the full profitability of vinylsilanes as viable precursors has yet to be realized.

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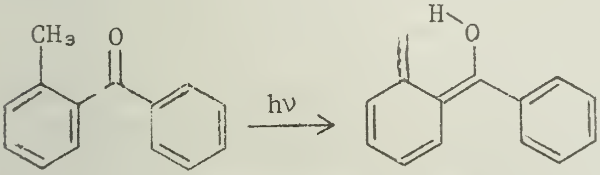
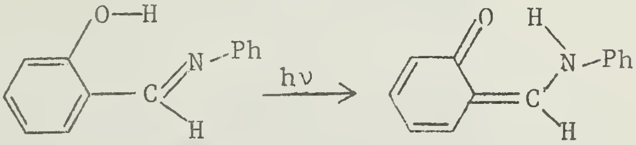
MECHANISTIC ASPECTS OF THE PHOTOTAUTOMERISM OF PHENOLS AND AROMATIC KETONES

Reported by Sander G. Mills　　　　October 27, 1980

The ability of aromatic systems such as 1 and 2 to tautomerize upon irradiation (to 1a and 2a respectively) has been widely studied in the last thirty years. Innumerable examples of these processes have been discovered in this time, and a variety of synthetic and technological applications demonstrated.[1,2] However, in most cases the mechanisms remained unclear. Recent work, using very fast kinetics techniques, theoretical models, and substituent effect studies have extended our understanding of these systems.



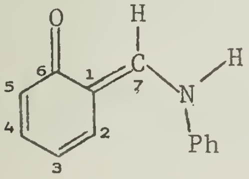
1　　1a



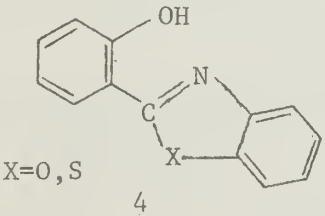
2　　2a

Phenol Derivatives. The first examples of phototautomerism came in the 1950's, based on the observation of unusually large shifts in fluorescence maxima in salicylic acid derivatives.[3] Shortly thereafter, Cohen and coworkers[4] reported that photochromic properties of salicyclidine anilines (anils) were also from tautomeric shifts (i.e., 2 → 2a).[4] These proton transfers could be rationalized qualitatively by noting that the acid-base properties of many functional groups shift strongly in the first excited singlet state.[5] Phenols, for instance, become more acidic and carbonyl groups more basic,[1b] facilitating the proton transfer. It was also shown that the H-bond between the donor and receptor sites was necessary, since the anil of p-hydroxy benzaldehyde was not photochromic.[6]

In the anils,[7] a further isomerization occurs to give 3, which is assumed to be the photochromic (colored) species.[4,6] Subsequent investigations[8,9] have established that, contrary to expectation, the vibrationally relaxed excited singlet cis-quinoid 2a does not appear to be the direct kinetic precursor to 3. Spectra of the conformationally more rigid system 4 showed similar behavior.[10] On the basis of these results, as well as semi-empirical calculations on the excited state surface of 2-2a,[11] it was suggested that the intermediate that partitioned between the cis and trans form of the quinone displayed a geometry twisted about both the C_1-C_7 bond and the C_7-N bond, which was postulated to occur only in a nonvibrationally relaxed level of the singlet excited state.[11] In nano- and picosecond studies of 2 and 4 (X=S), Rentzepis and coworkers[12] tentatively concluded that a transient observed at 4K (whose lifetime was only 7 psec) was this unrelaxed species, and supported this speculation with the viscosity[12] and excitation wavelength dependence of the fluorescence spectra.[11]



3

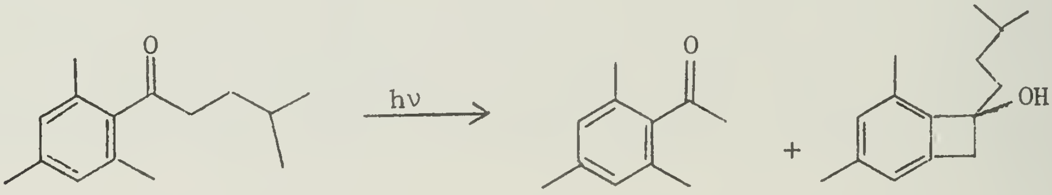


4

Aromatic Ketones. The photoreduction of benzophenone to benzapinacol, which proceeds through the $^3n,\pi^*$ state, displays a decreased product quantum yield when an ortho alkyl substituent is present.[1a] This has been attributed to the transformation 1 → 1a, and has been detected via ESR experiments and has been trapped by dienophiles. This process has been observed in other aryl and alkyl aryl ketones as well as o-alkyl benzaldehydes.[1a,13-18]

The results of flash photolyis studies on 1 have been in dispute.[19-22] Uji-Ie and coworkers[20] claimed that two non-interconverting ketone triplets led to the cis and trans dienols separately. Das et al.[21,22] interpreted the data in terms of a single triplet precursor to both products, supporting the assignment with measurements of the electron transfer properties of the biradical precursor.[22] Theoretical studies,[23,24] performed on cis-2-butenal (a model for the aromatic ketones) have been used to evaluate the energies of excited state structures, but their applicability to aromatic systems is limited by the neglect of steric factors in the larger systems.

In contrast to benzophenone derivatives, 2-alkylphenyl alkyl ketones show two distinct enol triplet precursors,[13,22] and these are assigned to the syn and anti conformers of the ketone triplet. As expected, the syn isomer has a much shorter lifetime because of the closeness between the oxygen and the labile hydrogen. 2,6-dialkylphenyl ketones, also studied by these authors,[13,22] gave complex results. Wagner[13] studied the competition between type II photoelimination and ortho proton abstraction in 5. He could not rationalize the kinetics, solvent data, and quencher behavior with a simple model, but speculated that it may involve the geometry dependent equilibration between triplet n,π^* and π,π^* states lying fairly close in energy.[25]



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TWO DIMENSIONAL NUCLEAR MAGNETIC RESONANCE AND SOME APPLICATIONS IN ORGANIC CHEMISTRY

Reported by Tuyen T. Nguyen November 3, 1980

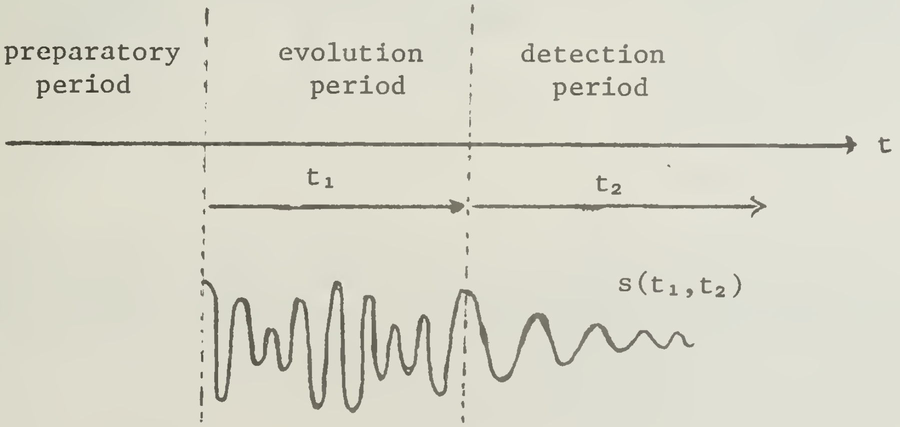
Nuclear Magnetic Resonance (NMR) spectroscopy has been a very useful tool for structural determination of organic molecules. However, with complex molecules it is sometimes not possible to make a complete assignment of the investigated spectrum. The recent development of the two-dimensional (2D) NMR,[1] in which chemical shift and spin coupling in weakly coupled spin systems are separated, provides a new way to analyze the complex spectra of organic molecules such as those of carbohydrates and steroids.

The 2D NMR spectroscopy involves a plot of spectral data where both variables are frequencies.[2] By definition, the stacking of a set of spectra as a function of time in a two dimensional manner is not considered a two-dimensional spectrum. In general, a signal $s(t_1,t_2)$, which is a function of two time variables t_1 and t_2, can be transformed into a signal S, which is a function of two frequencies ω_1 and ω_2, by a two dimensional Fourier transformation:

$$S(\omega_1,\omega_2) = \hat{F}_{t_1,t_2}[s(t_1,t_2)]$$

The 2D NMR spectrum is obtained this way. To introduce the two independent time variables, t_1 and t_2, the time axis is divided into three periods: preparatory, evolution and detection periods. In the preparatory period, the system is prepared to give a suitable initial state. The system evolves under the influence of a Hamiltonian H_1 in the evolution period. At the end of this period the system will have a particular state that depends on H_1 and the elapsed time t_1. The time variable t_1 is the length of the evolution period, and t_2 is the running time of the detection period. The resulting signal $s(t_1,t_2)$ is the function of both time variables as presented in Figure 1.

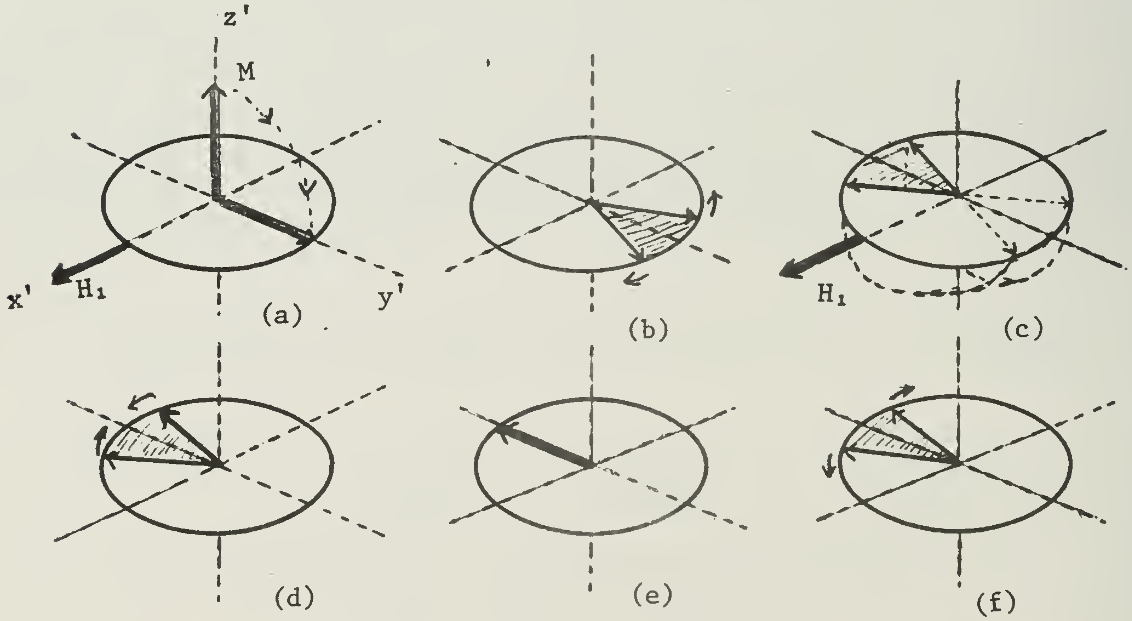
Figure 1. The basic principle of 2 dimensional spectroscopy [2]



Based on this principle, many kinds of 2D spectra can be generated. In this seminar, we are concerned only with 2D spectroscopy of proton, and proton-coupled carbon-13.

The Carr-Purcell experiment.[3] The Carr-Purcell spin-echo experiment is the basis of 2D spectroscopy. This experiment uses two radiofrequency (rf) pulses that have the magnetic component perpendicular to the macroscopic magnetic moment M which is the sum of all the magnetic moments M of nuclei in the sample. In the rotating frame of reference, a coordinate system in which the x' and y' axis rotate synchronously with the radiofrequency field around the z' axis, which is in the direction of the external magnetic field, a 90° rf pulse in the x' direction will tip M onto the y' axis (as shown in Figure 2a). As a result of field inhomogeneity in the external field, some magnetic component M's precess faster than ω and some precess slower. Therefore, in the rotating frame of reference, magnetic components M begin to fan out in 2b. After a time τ, the transverse decaying magnetization is reflected into its mirror image (relative to the x'z' plane) by a 180° pulse, as shown in 2c. At time 2τ, all the components will converge (2d) to give an echo (2e), and then they will fan out again (2f). Therefore after the 90°

Figure 2. The basis of the Carr-Purcell spin-echoes experiment

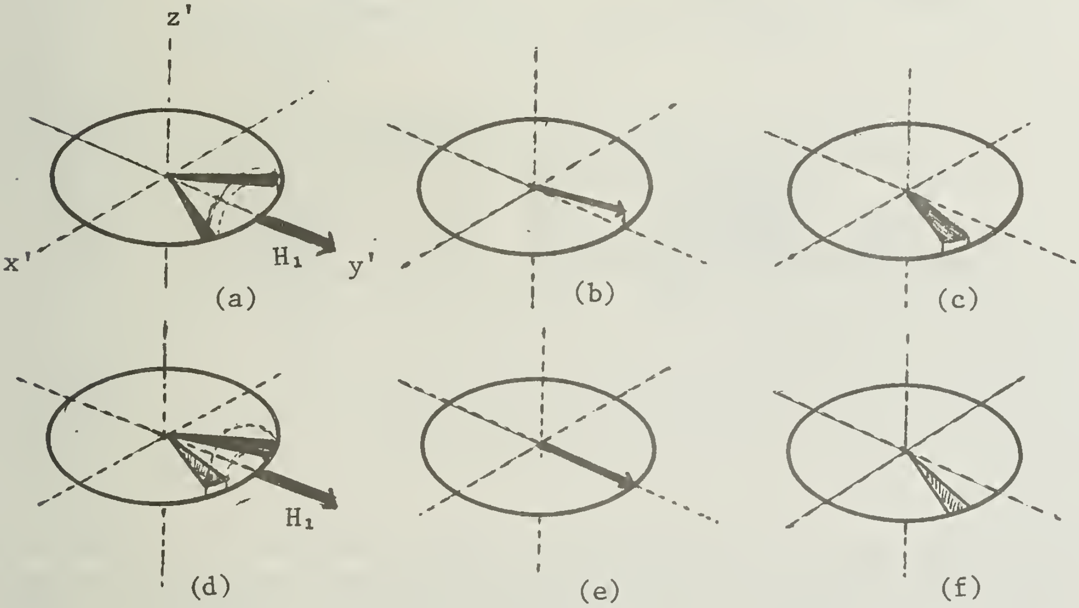


(a) Magnetization M is flipped onto the y' axis by H_1.
(b) Its components spread out due to the external field inhomogeneity.
(c) Conversion to the mirror image by H_1.
(d) Refocussing of M which gives an echo in (e).
(f) Components spread out afterward.

pulse, 180° pulses at τ, 3τ, 5τ... will produce echoes at 2τ, 4τ, 6τ....

In practice, a 90° or a 180° pulse is produced empirically to give best echoes. A small inaccuracy of the 180° pulse will eventually lead the magnetization out of the x'y' plane. Meiboom and Gill[4] suggested the 180° pulse to be applied along the y' axis. This modification corrects the problem of the Carr-Purcell experiment. It is illustrated in a sequence of figures (3a-3f) analogous to those of 2 except that the 180° pulse is applied above the y' axis.

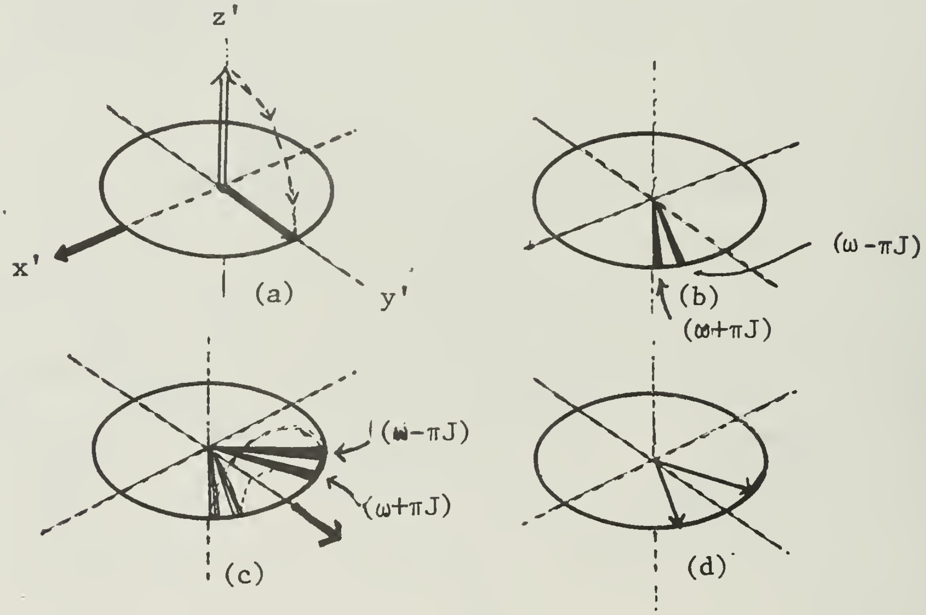
Figure 3. The Meiboom-Gill experiment



(a) A pulse slightly smaller than 180° will focus M above the x'y' plane in (b). The magnetizations spread out above the xy plane in (c). The same pulse puts the magnetization on the x'y' plane (d) which gives an echo in (e). The process continues in (f).

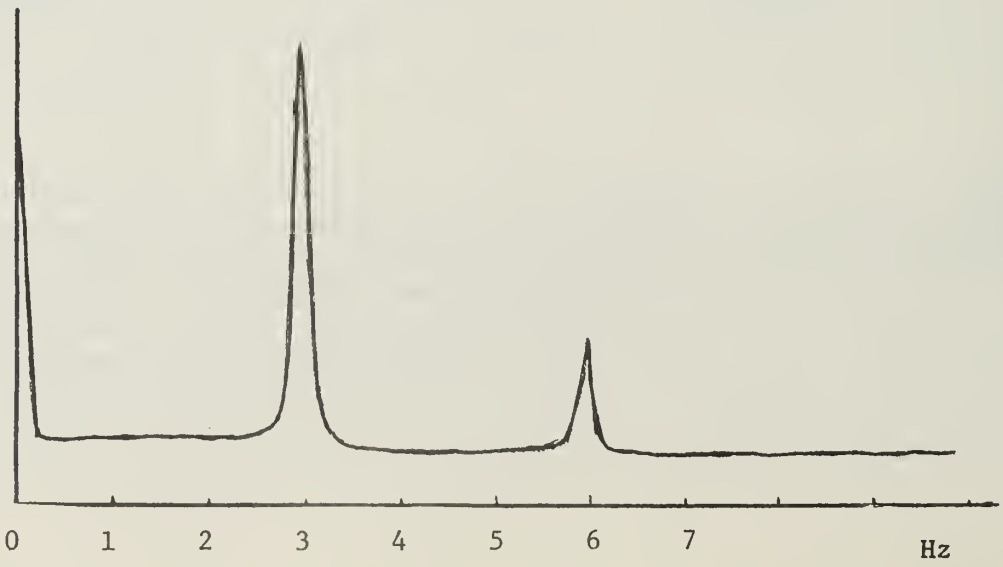
Echo modulation.[5] Echo modulation or J modulation occurs when a single spin species A is weakly coupled by J Hz ($2\pi J$ radsec^{-1}) to another nucleus of the same species X. The rf pulses affect both nuclei. In the reference frame rotating at the radio frequency, after the initial 90° pulse, the magnetization will split into two components centered about the positions $(\omega + \pi J)T$ and $(\omega - \pi J)T$. When the 180° refocussing pulse is applied (as in the Meiboom-Gill experiment), the mirror image of the two components are formed, but the pulse also simultaneously rotates the magnetization of X so the two components are also interchanged. At time $t=2\tau$, two discrete components are observed. This phenomenon is illustrated in Figure 4.

Figure 4. Effect of homonuclear spin-spin coupling in the Carr-Purcell-Meiboom-Gill experiment



If the 180° pulses are applied in a sequence at time τ, 3τ, 5τ,... echoes will form at 2τ, 4τ,.... The amplitude of the echoes will decay gradually due to spin-spin relaxation. Fourier transformation of the echoes that are obtained at 2τ, 4τ,... will give a J spectrum which shows only the effect of spin coupling. An example of a J spectrum is shown in Figure 5.

Figure 5. The J-spectrum of $CH_2ClCHCl$



Homonuclear 2D spectroscopy.[1] The homonuclear (^{1}H-^{1}H) 2D spectroscopy can be obtained in the following ways. The 90° pulse in the x' direction starts the evolution period (t_1). At $\tau(1/2\ t_1=\tau)$ seconds later, a 180° refocussing pulse is introduced which will give a spin-echo at t_1 or 2τ. The free decay of this echo is then sampled. A large number of free decaying echoes are collected with t_1 systematically varied. Fourier transformation of this set of data yields a two dimensional spectrum. The amplitudes of the spin-echoes are affected only by spin-spin coupling constants and the relaxation process. Therefore, multiple splitting will be seen in the ω_1 direction while all the resonance absorptions will be contained in the ω_2 direction. The basic scheme for 2D J spectroscopy is illustrated in Figure 6. An example of a proton 2D spectrum is shown in Figure 7.

Figure 6. Basic scheme of proton 2D NMR

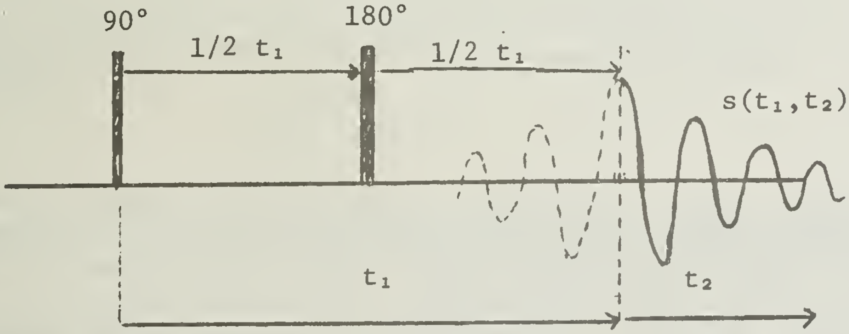
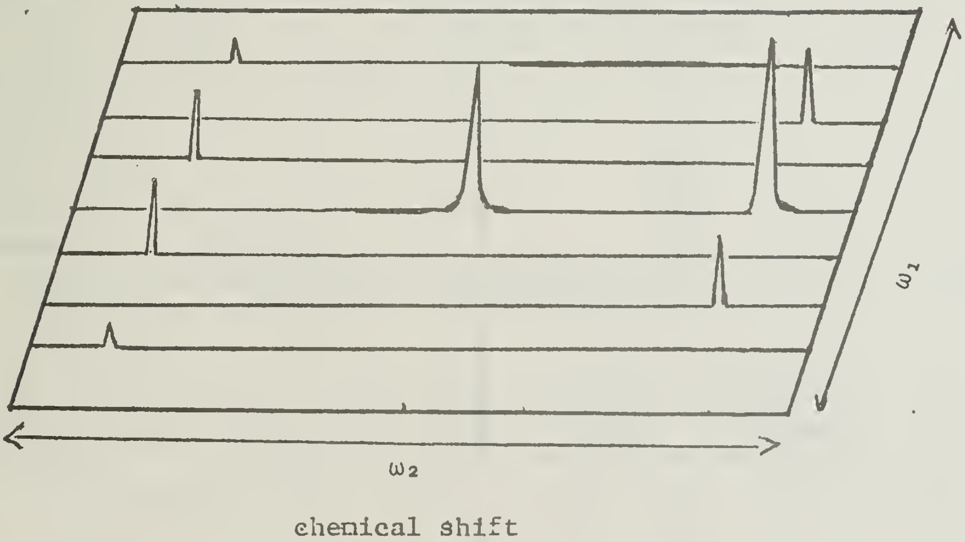
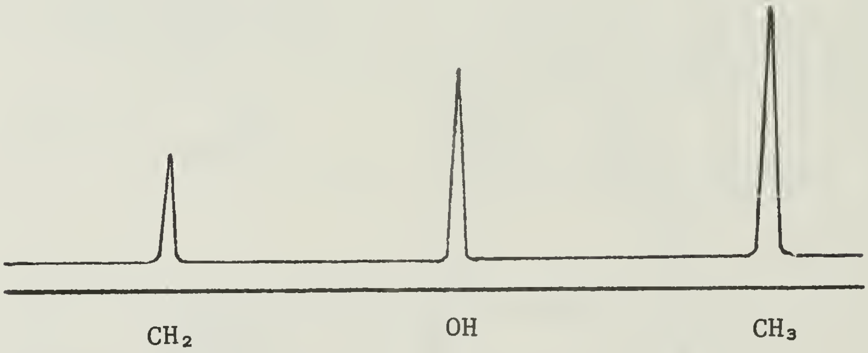


Figure 7. A "rough" spectrum of CH_3CH_2OH



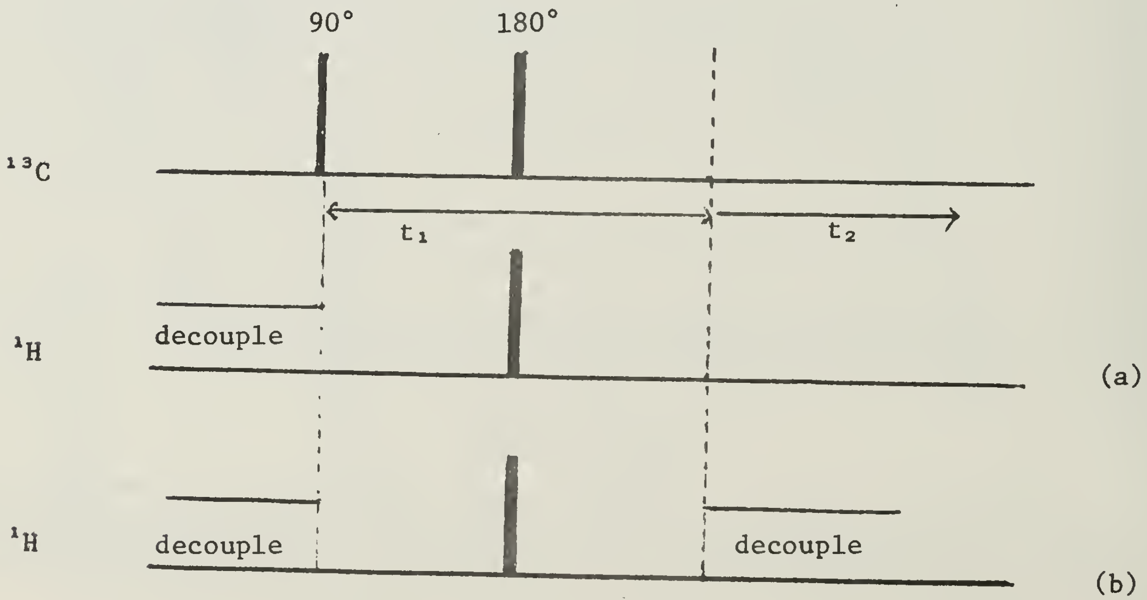
It should be noted that peaks of every multiple are on a straight line, therefore a projection along a line 45° from the ω_2 axis, in a procedure which is described by Nagayama and Ernst,[6] will give a completely decoupled spectrum. This is basically a way to obtain a proton spectrum with broad band proton decoupling (Figure 8).

Figure 8. Projection of the 2D spectra of CH_3CH_2OH onto the ω_2 axis at 45° angle gives proton-decoupled proton spectrum



Heteronuclear (^1H-^{13}C) 2D J-spectroscopy.[7] There are several ways to obtain proton-coupled ^{13}C spectra. Let us consider the method that involves a "proton flip." This method also utilizes two pulses, 90° and 180°, this time at the ^{13}C resonance frequency. The detection period, as before, starts at time 2τ. However, the 180° pulse at the carbon resonance frequency will not invert the spin state of proton(s) coupled to the carbon atom. Therefore, no J modulation occurs. To introduce this J modulation, a 180° pulse, which

Figure 9. Two basic methods to obtain a 2D spectra of ^{13}C NMR Method (a) gives coupling information in both ω_1 and ω_2 dimensions. Method (b) gives coupling information only in the ω_1 dimension.



is synchronized with the other 180° pulse, is applied simultaneously into the decoupling channel. This pulse inverts the spin state of the proton, thus J modulation occurs. At the preparation period, all protons are radiated to establish a nuclear Overhauser effect.[8] At the detection period, if the protons are radiated (as in 9b), only chemical shift is contained in the t_2 dimension. In this case, after the Fourier transformation, we have the 2D ^{13}C spectrum which has chemical shift in ω_2 dimension and $^1H-^{13}C$ coupling in ω_1 dimension. If the protons are not decoupled in the detection period (in 9a), a full undecoupled ^{13}C spectrum is seen in the ω_2 dimension.

Applications. Two dimensional J-spectroscopy has been used to assign chemical shifts and coupling constants of protons in various classes of compounds. These include nucleoside monophosphates,[9] peptides,[10] mono- and disaccharides,[11] and steroids.[12] Usually the assignments are made based on 2D spectra only. However relaxation rates, nuclear Overhauser enhancement differences, and decoupling difference techniques are also used in the more complex molecules. An example of this is the analysis of proton NMR spectrum of 1-dehydrotestosterone.[12] Recent improvement in the shortening of the measuring time[13] enhances the usefulness of 2D J-spectroscopy in solving complicated spectra.

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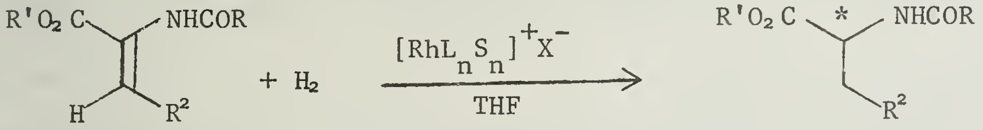
ASYMMETRIC CATALYTIC HYDROGENATION OF PROCHIRAL AMINO ACID PRECURSORS

Reported by Jack Muskopf November 6, 1980

The homogenous asymmetric hydrogenation of prochiral olefins catalyzed by chiral rhodium(I) complexes is an important synthetic method.[1] Although simple olefins generally give low optical yields (less than 50% ee), much better results (optical yields greater than 90% ee) have been obtained for the reduction of (Z)-α-N-Acylamidoacrylic acids and esters, forming amino acid derivatives (Eq. 1).[1-5] The chiral rhodium(I) catalyst, prior to addition of the prochiral amino acid precursor, is typically of the form $[RhL_nS_n]^+X^-$, where L is a chiral phosphine ligand and S is a solvent molecule. The optical yields of 80-99% ee found for the asymmetric reduction of (Z)-α-N-Acylamido acrylic acids and esters have led to a number of studies dealing with substrate specificity,[17] asymmetric induction and finally, determination of the individual steps in the overall mechanism. This review will focus on these studies.



(1)

*chiral center

The ability of a chiral catalyst to effect high optical yields is thought to be a function of the rigidity of the ligand-metal complex.[4a] Generally low optical yields are obtained when the phosphine is unidentate while bidentate ligands give better results.[1b] Ligands in which the chirality resides on the phosphorus atoms[3] or the carbon chain[4,7] have given equally good results.[1] Bosnich has recently provided evidence that the success of these chiral bidentate ligands can be traced to the chiral array of quasi-axial and quasi-equatorial substituents on the chelating phosphorus atoms.[4,6]

It is known that (Z)-α-N-Acylamidoacrylic acids and esters give much higher optical yields of reduced products than the corresponding E isomer.[3] Separate studies by Knowles[9] and Kagan[10] have addressed this phenomena, each using deuterium labeling as a method of determining the reaction pathway. Both studies concluded that E to Z isomerization was the cause of decreased optical yield for the E isomer, although each group postulated a different isomerization mechanism.

A detailed reaction mechanism has recently been reported by Halpern based on comparison studies of the hydrogenation of alkyl (Z)-α-N-Acetamidocinnamates in methanol, using either the chiral complex [Rh(S,S-Chiraphos)]$^+$ or the achiral [Rh(diphos)]$^+$ as the homogenous catalyst.[11-14] Examination of the rate data and identification of several intermediates led to the conclusion that the enantioselectivity of these reactions was determined by the rate of hydrogen addition to the diastereomeric catalyst-substrate adducts and not by the preferred mode of binding of the prochiral olefin to the chiral catalyst.[15] This interpretation provides an explanation for the inverse dependence of optical yield on the partial pressure of hydrogen observed in similar systems.[3,14,16]

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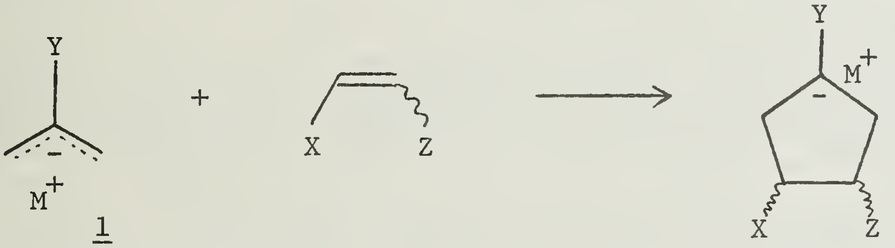
NEW 2-SUBSTITUTED ALLYL ANIONS: β' LITHIATION OF α,β-UNSATURATED SECONDARY AMIDES

Reported by Dale Kempf November 10, 1980

The synthetic potential of 2-substituted allylic carbanions has only begun to be realized. A number of examples have appeared in the literature including those in which the substituent Y (anion 1) is formally alkyl,[1] phenyl,[2] CN,[3] $SiMe_3$,[4] $CONR_2$,[5] CH_2OLi,[6] CO_2R,[7] COR,[8] O^-,[9] CH_2Li,[10] and most recently, CONLiR.[11,12] For best synthetic utility, Y should be (a) inert to the conditions used for preparing the anion and (b) easily transformed to other functional groups in later steps. In addition, for some reactions it is preferable for Y to be electron withdrawing.

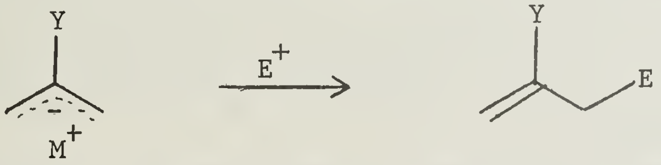
2-substituted allyl anions have been generated by conrotatory ring opening of cyclopropyl anions[13] and by metal-halogen or metal-oxygen exchange of allylic halides and ethers. A more general method, however, is through direct deprotonation of 2-substituted propenes, since electron withdrawing groups at the termini are required for ring opening[14] and more complex precursors are required for the exchange reactions. A few of the anions generated by deprotonation require additional activation at the 1 and 3 positions as well.

The anions thus prepared have often been used with olefins in 1,3-anionic cycloadditions to give cyclopentanes (Eq. 1).[2a-c,3,15] First noted in the reactions of allylic Grignards with benzyne,[4,16] the cycloaddition may be concerted in some instances,[3b] but has been shown to be stepwise in one case.[5] Activated olefins and an electron withdrawing substituent (CN, Ph, $CONR_2$) at the 2-position of the anion are required for the cycloaddition to progress, the latter in order to stabilize the anionic product.



(1)

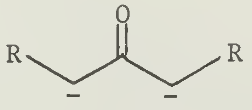
Trapping the allyl anions at one of the termini results in electrophilic substitution at that position (Eq. 2). Reaction with aldehydes and ketones leads to α-methylene butyrolactones when Y is of the acid oxidation level.[6a,7a,b]



(2)

The anions have also been trapped with alkyl and trialkylsilyl halides to give noncyclized products.[1d,2d,6b,7c] Several 2-alkyl allyl anions have been employed as isoprenyl anion synthons.[1a-d]

Special examples of 2-substituted allyl anions include α,α' ketone dianions (2) and the trimethylenemethane dianion (3). Ketone dianions have been found to be much more nucleophilic than their enolate precursors though somewhat less selective.[9] The trimethylenemethane dianion has recently been shown to be synthetically as well as theoretically useful.[10]



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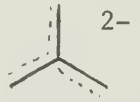
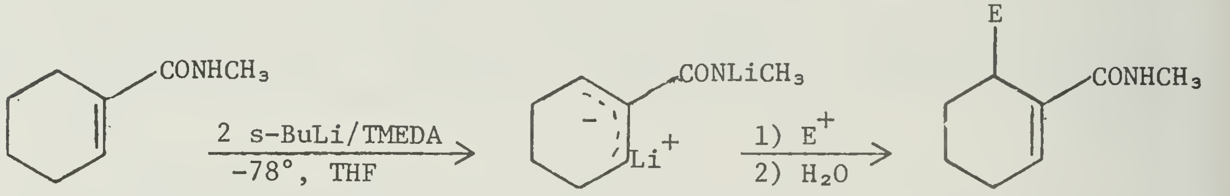


3

The 2-substituted allyl anions which appear to be the most promising synthetically are those derived from α,β-unsaturated secondary amides.[11] Amides can be readily converted to other functionalities, and initial deprotonation deactivates the carbonyl group toward nucleophilic attack. Most important, the strong directing ability of the secondary amide monoanion[17] enables β' proton removal in the presence of potentially acidic β and γ hydrogens.[18] As shown in Eq. 3, the dianion formed from N-methyl-1-cyclohexene-carboxamide can be trapped with a number of different electrophiles in synthetically useful yields. The deprotonation is also selectively β' in five-membered and acyclic cases.[11,12] Reaction with ketones followed by cyclization leads to the corresponding α-alkylidene butyrolactones.[11,12]



$E^+ = CH_3OD$, $CH_3(CH_2)_5Br$, CO_2, $(CH_3)_2CO$, Ph_2CO, $(n\text{-}Bu)_3SnCl$

The synthetic potential of these amide dianions appears to be quite high due to the selectivity observed in deprotonation. However, regioselectivity in the subsequent reactions with electrophiles can be a problem if the allylic system is unsymmetrically substituted and isomeric mixtures can be formed.[11] Furthermore, the reaction conditions appear to be important, since some substituted acryanilides have been shown to serve as Michael acceptors with alkyl and aryllithium bases.[19]

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THE UGI REACTION

Reported by Jim Gloer November 13, 1980

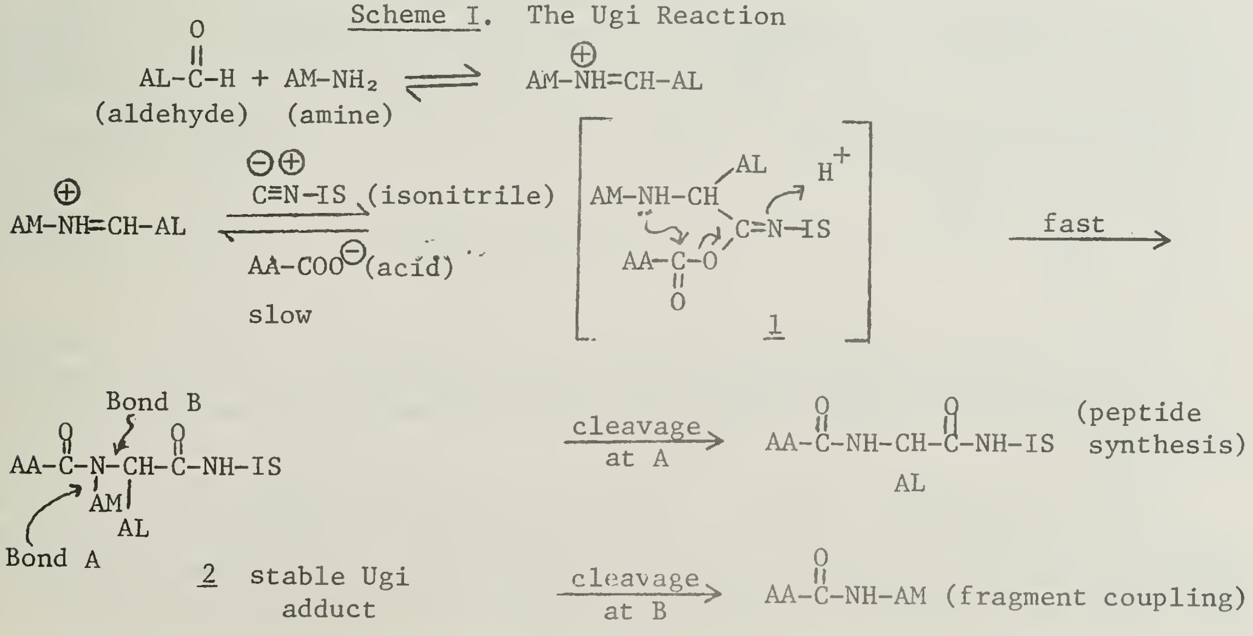
Classical methods for peptide synthesis involve amide bond formation by reaction of an acylating derivative of an N-terminally protected α-amino acid with the α-amino group of a C-terminally protected component.[1] Fragment coupling, the technique of choice for making large peptides, is also achieved in this manner. Although these methods are often adequate, problems are frequently encountered in the areas of side reaction, racemization, yield, and hence purification.

The Ugi Reaction[2] (Four Component Condensation) offers an alternative approach to peptide synthesis and fragment coupling which has already demonstrated potential in dealing with these difficulties.[3] The most important application of the Ugi Reaction to peptide chemistry is in the area of fragment coupling. It has allowed the coupling of two peptide fragments to occur in good yield with essentially no racemization.[4,5,27]

This review will examine the Ugi Reaction and its advantages over classical techniques. A discussion of the problems encountered in employing this method as well as their possible solutions will be included. In addition to this, other useful syntheses utilizing the Ugi Reaction will be outlined.

The Reaction. The Ugi Reaction in this context (Scheme I) involves the condensation of four components: a primary amine, an aldehyde, an acid, and an isonitrile, and may be viewed as a cross between a Mannich Reaction and a Passerini Reaction.[6] The mechanism[7] involves initial condensation of the amine with the aldehyde to give the Schiff base, which is protonated in the presence of acid. This species and the carboxylate anion then react with the terminal carbon of the isonitrile via a series of equilibria to give the usually non-isolable intermediate 1,[8] which rapidly rearranges by a cyclic, first order pathway to afford the stable adduct 2. Depending on the choice of components, the reaction product may then be cleaved at bond A to give a new peptide or at bond B, which results only in the coupling of the acid and the amine.

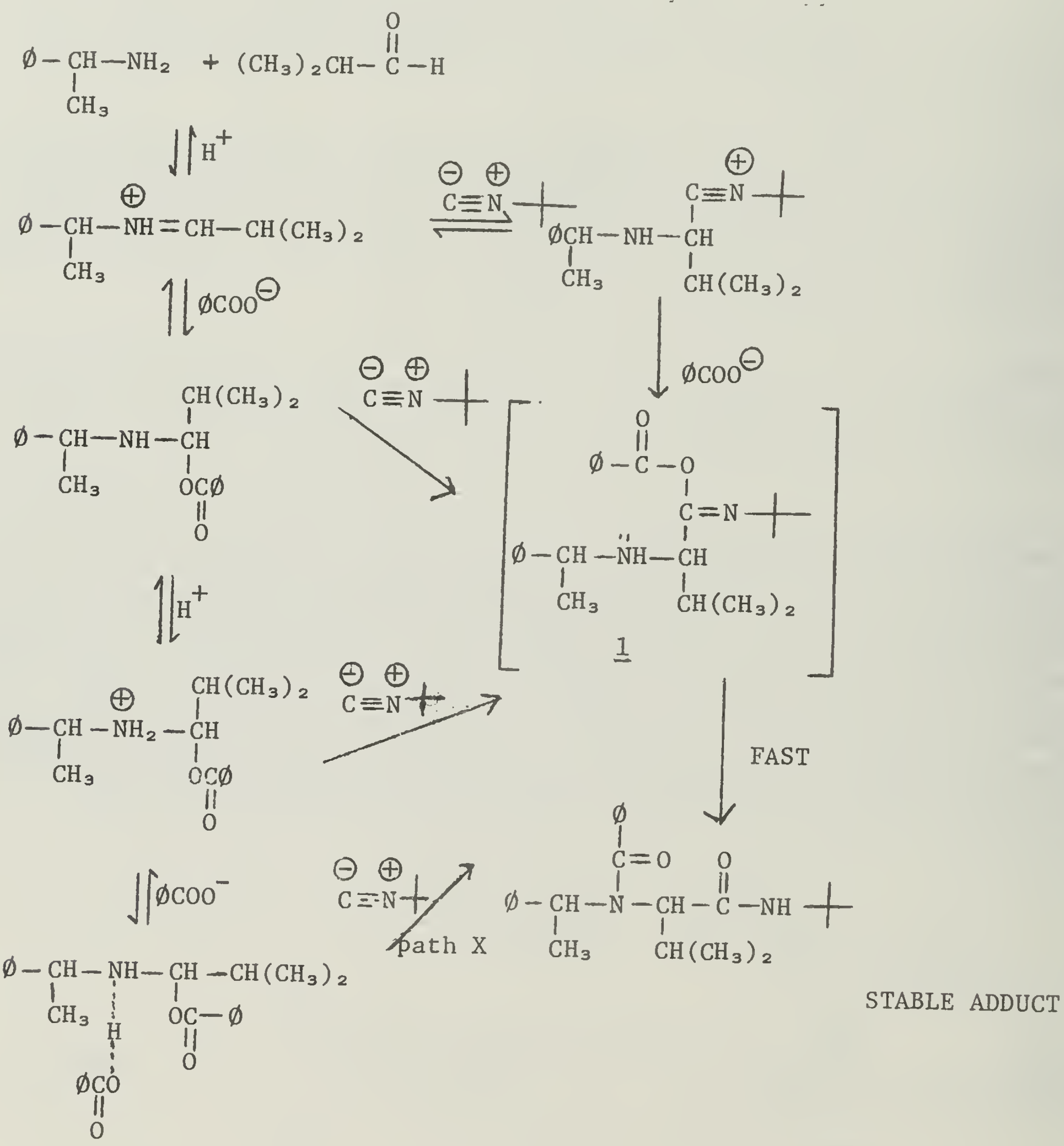
Scheme I. The Ugi Reaction



AL-C(=O)-H + AM-NH₂ ⇌ AM-NH⁺=CH-AL
(aldehyde) (amine)
AM-NH⁺=CH-AL
⁻C≡N⁺-IS (isonitrile)
AA-COO⁻ (acid)
slow
AM-NH-CH(AL)-C=N-IS, AA-C(=O)-O, H⁺
1
fast
Bond B
Bond A
AA-C(=O)-N(AM)-CH(AL)-C(=O)-NH-IS
2 stable Ugi adduct
cleavage at A
AA-C(=O)-NH-CH(AL)-C(=O)-NH-IS (peptide synthesis)
cleavage at B
AA-C(=O)-NH-AM (fragment coupling)

A closer examination of the route leading to formation of 2 has established that the mechanism is complex, involving a series of four alternative ways to form 1 (Scheme Ia). A further complication is introduced by the fact that the intermediates in each pathway are in dynamic equilibrium with all the other intermediates in the other pathways, so that the kinetics of the reaction are not trivial.[9]

Scheme Ia. Mechanism of the Ugi Reaction

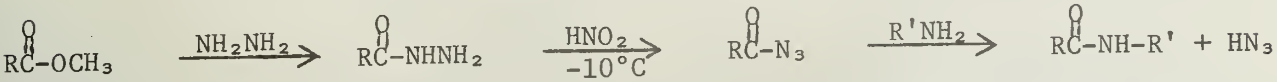


The scope of the Ugi Reaction is by no means limited to peptide chemistry. Some other aspects of this versatile synthetic method are discussed later in this abstract.

Peptide Synthesis. The most widely used methods of peptide synthesis are based on the use of carboxyl group-activated amino acids or the use of coupling reagents, which both function by similar mechanisms.[1] Many of these methods have been used for decades and have proven reliable and useful, but all have their drawbacks. The azide method, for example, (Scheme II), developed by

Curtius in 1902, allows formation of peptide bonds with very little racemization. However, the intermediate hydrazide and the azide itself are susceptible to substantial side reactions, such as amide formation and Curtius rearrangements.[1] Dicyclohexylcarbodiimide is the most widely used coupling

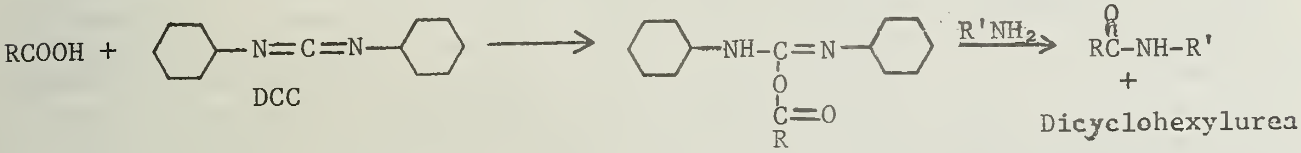
Scheme II. The Azide Method.



$$\mathrm{R\overset{O}{\overset{\|}{C}}\text{-}OCH_3 \xrightarrow{NH_2NH_2} R\overset{O}{\overset{\|}{C}}\text{-}NHNH_2 \xrightarrow[-10^\circ C]{HNO_2} R\overset{O}{\overset{\|}{C}}\text{-}N_3 \xrightarrow{R'NH_2} R\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}R' + HN_3}$$

reagent (Scheme III). It gives good yields with minimal side reactions, but racemization is a problem, even in the presence of N-hydroxysuccinimide.[1,10]

Scheme III. Amino Acid Coupling with Dicyclohexylcarbodiimide (DCC)



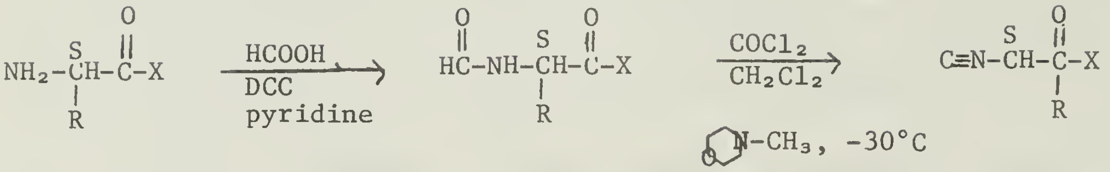
All of these methods also involve protection of N- and C-termini as well as many of the common amino acid residues, followed by deprotection to allow reaction with the next protected amino acid to be added onto the chain. Consequently, several steps are required to add each amino acyl residue.

Application of the Ugi Reaction to peptide synthesis (Scheme I) has several advantages over classical techniques. Fewer steps are involved in synthesis by this method. Two new peptide bonds and an extra amino acyl unit are formed in effectively one step, and the only functional groups which require protection are COOH, NH_2, and SH.[3] Unusual amino acids which do not occur in nature or are difficult to synthesize (e.g., isotopically labelled, sterically hindered) might be easily incorporated into a peptide by Ugi Reaction via their aldehydes.[3,7] α-alkyl amino acids are accessible through the appropriate ketones.[11]

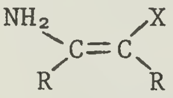
Peptide bond formation by the Ugi Reaction is a unimolecular process, as opposed to classical methods of peptide bond formation which involve bimolecular reactions. The formation of the peptide bonds from the acylating intermediate 1 is much faster than classical bimolecular peptide bond formation. The rearrangement of 1 to give 2 occurs after the rate determining steps[7] and no products of intermolecular reactions involving 1 have been isolated. Advantages stemming from this include the occurrence of fewer side reactions and less racemization, hence, purification problems are less pronounced than those of classical methods.

Unfortunately, this method introduces new problems which have yet to be completely solved. For the reaction to yield an optically pure product, one must start with an optically pure isonitrile. Stereospecific synthesis of α-isocyanoacid derivatives is troublesome, but has been accomplished in some instances by dehydration of the N-formyl-t-butyl esters[12] with phosgene at temperatures below -20°C in the presence of N-methylmorpholine (Scheme IV).[12,13] The isocyano group is more easily introduced into a fragment in which the carbonyl is that of an amide, because the anionic intermediate leading to racemization is not formed as readily.[3] In fact, dipeptides and oligopeptides pose little problem in their stereospecific conversion to isonitriles.

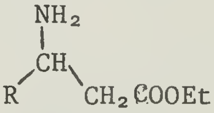
Scheme IV



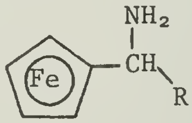
A more difficult problem is that of the amine component. Its structure must be such that bond A (Scheme I) is easily severed, but it must also be able to perpetrate asymmetric induction on the new α-carbon if we wish to designate the stereochemistry there. Three classes of amines which have potential to satisfy these conditions have been investigated.[14] Ugi adducts of resonance stabilized vinyl amines (3) easily cleave under mild conditions, but can possess little asymmetric inducing power because any chiral elements would have to be relatively far away from the forming chiral center. β-alanine derivatives (4) demonstrate good stereoselectivity, but cleavage is effected only by strong base, which can damage a peptide and promote racemization.[1] The best solution to the problem so far involves the use of chiral α-ferrocenyl alkylamines (5).[3,7,16] The obtained adducts (e.g., 6 and 7) are formed in good yield and are easily cleavable due to facile formation of α-ferrocenylcarbonium ions.[15] The proximity of the chiral center to the site of the forming chiral center allows >90% stereoselectivity to be achieved under proper conditions.



3 (X=CN, COOEt)



4 (R=Ph, Ar)



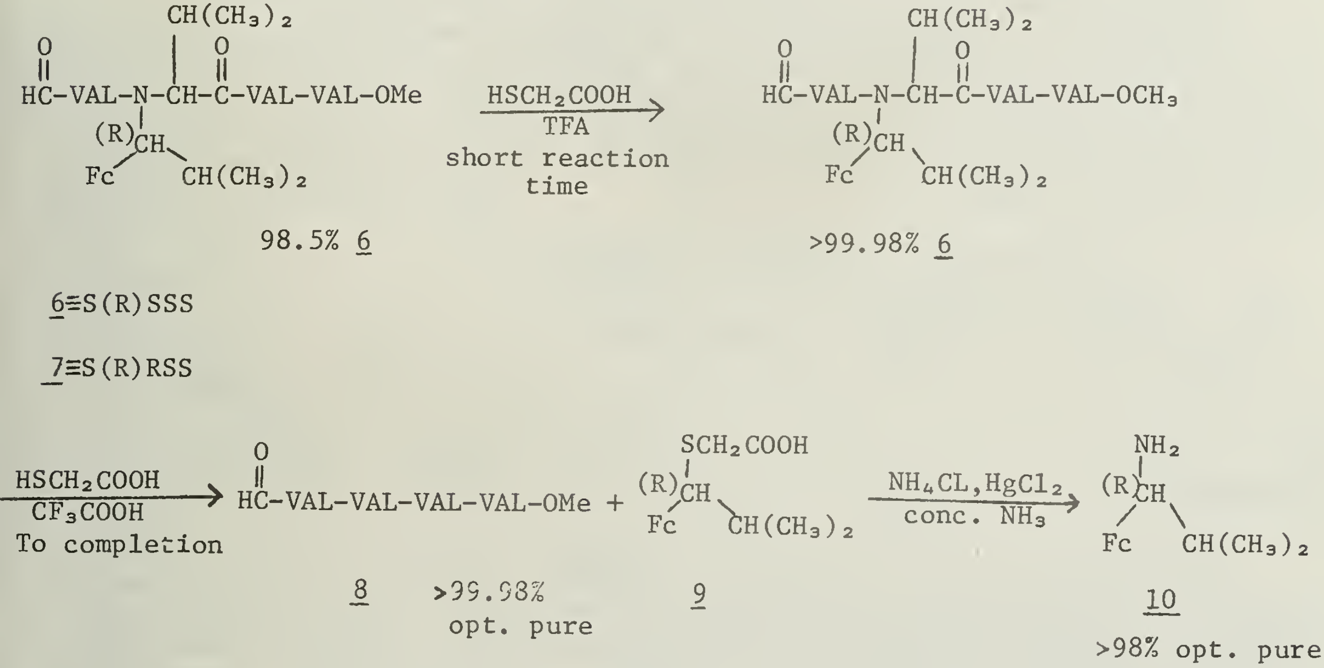
5 (R=alkyl)

Each of the alternative pathways in Scheme Ia has a different propensity towards stereoselectivity. If the conditions are chosen to favor the most selective pathway, then the stereoselectivity will be optimized. The reaction in Scheme Ia (with S-α-phenylethylamine) was carried out 264 times under various conditions which influence the concentrations of the intermediates in Scheme Ia.[9] It was concluded that maximum amounts of S,S diastereomer were obtained when the reaction was made to proceed through the nitrilium ion. Maximum S,R diastereomer was obtained when the reaction proceeded mainly via path X. These trends hold for chiral α-ferrocenylalkylamines and allow the selection of optimum reaction conditions for maximum stereoselectivity. This observed stereoselectivity can be influenced by addition of ammonium salts of the acid component and enhanced by selective acidolysis.[16]

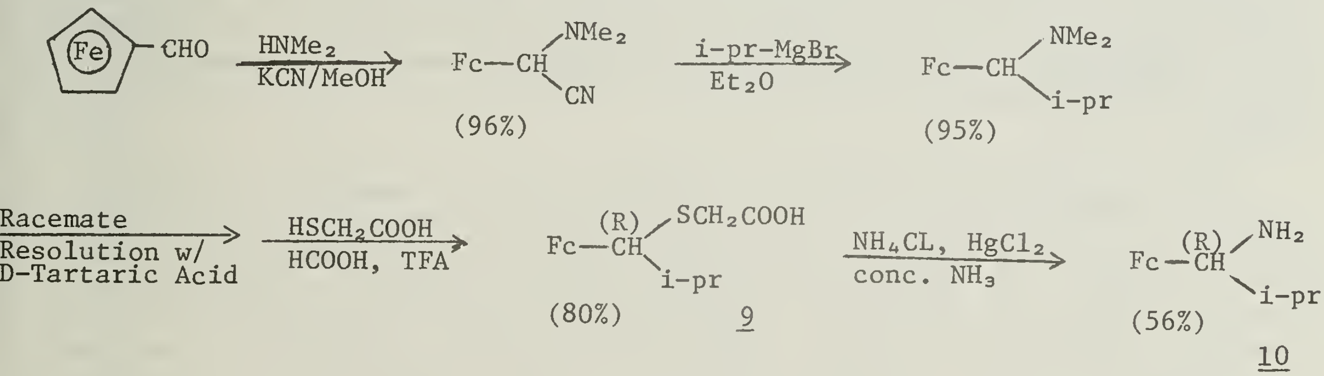
An Ugi Reaction of N-formyl-L-valine with R-1-ferrocenyl-2-methylpropanamine, 2-methylpropanal, and N-(2-isocyano-3-methylbutanoyl)-L-valine gives products 6 and 7 in the ratio 91.2:8.8. Addition of two equivalents of tetraethylammonium N-formyl-L-valinate increases the ratio to 98.5:1.5. Selective acidolysis (Scheme V) of this mixture for 1.5 hr followed by recovery of unreacted material increases the ratio to >99.98:0.02 with a loss of only 4.2% of 6.[16] 6 can then be cleaved to give essentially optically pure 8 in 73% overall yield.

The chiral α-ferrocenylalkylamines necessary for the reaction are accessible via the synthetic route outlined in Scheme VI.[22] If the Ugi Reaction products are cleaved with thioglycolic acid/TFA, the chiral product 9 and the subsequently regenerated α-ferrocenylalkylamine[17] 10 (Scheme V) both result from retentive S_NI reactions.[18] The reaction is observed experimentally to be first order and the retentive mechanism can be attributed to participation of the ferrocenyl group in the stabilization of the carbonium ion.

Scheme V. (Fc=ferrocenyl)


HC-VAL-N-CH-C-VAL-VAL-OMe
CH(CH₃)₂
(R)CH
Fc
CH(CH₃)₂
HSCH₂COOH
TFA
short reaction time
HC-VAL-N-CH-C-VAL-VAL-OCH₃
98.5% 6
>99.98% 6
6≡S(R)SSS
7≡S(R)RSS
HSCH₂COOH
CF₃COOH
To completion
HC-VAL-VAL-VAL-VAL-OMe
8
>99.98% opt. pure
SCH₂COOH
9
NH₄CL,HgCl₂
conc. NH₃
NH₂
10
>98% opt. pure

Scheme VI. (Fc=ferrocenyl)

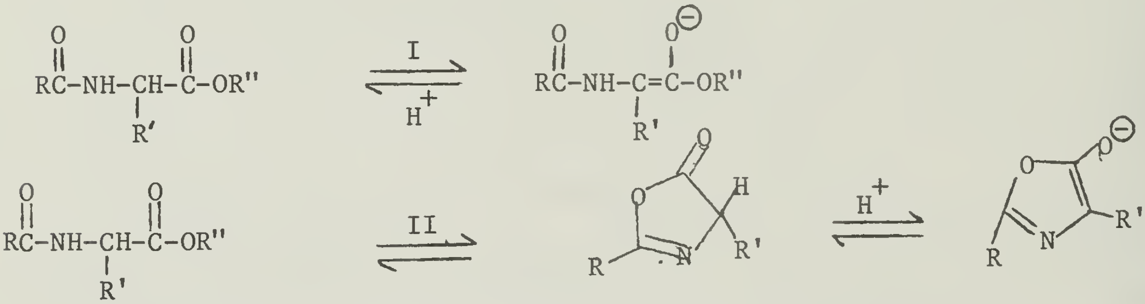

Fe
CHO
HNMe₂
KCN/MeOH
Fc—CH
NMe₂
CN
(96%)
i-pr-MgBr
Et₂O
i-pr
(95%)
Racemate
Resolution w/ D-Tartaric Acid
HSCH₂COOH
HCOOH, TFA
(R)
SCH₂COOH
(80%)
9
NH₄CL, HgCl₂
conc. NH₃
NH₂
(56%)
10

Experimentation with this method has focussed on the synthesis of small model compounds, but some small peptides have been made. The synthesis of optically pure glutathione[19] and the tetravaline derivative (vide supra) are noteworthy examples. Also of interest is the use of formaldehyde as the aldehyde component.[4,20] The new amino acyl unit in this case is glycyl, which requires no asymmetric influence. This ploy has been used in the synthesis of melanocyte inhibiting factor analogs.[20]

Fragment Coupling. An alternative for the synthesis of large peptides and proteins involves the synthesis of smaller fragments followed by the splicing together of these pieces.[1] This technique was employed in the first synthesis of a protein over 100 residues in length[21] and will undoubtedly be the method of choice in the future in synthesis of such compounds.

Large fragment coupling by classical methods is hindered primarily by the requirement that the reaction be second order. Collisions between the sites of reaction are very infrequent due to fragment size and low concentrations. Side reactions, particularly racemization (Scheme VII), which are often first order (or pseudo first order), compete very effectively with the desired reaction. Racemization of the acylating peptide fragment can occur either by direct proton loss from the α-carbon (path I) or, more likely, via azlactone enolate formation (path II).[1]

Scheme VII



Application of the Ugi Reaction to fragment coupling (cleavage at bond B, Scheme I) seems capable of surmounting these obstacles. Intramolecular, rapid formation of the peptide bond is the main reason for the potential superiority of the Ugi Reaction over conventional methods. Racemization cannot occur until the intermediate 1 (Scheme I) is formed. Once 1 is formed, the proximity of the reacting groups assists very rapid rearrangement to 2, which cannot racemize. Thus minimized racemization (and side reactions) can be attributed to the fleeting existence of 1, in contrast to the relatively lengthy time that the c-terminally activated fragment exists in conventional syntheses. An additional boon of this method is the solubility of the adduct 2 and the cleavage byproducts in organic solvents, facilitating isolation of the final peptide derivative.[22]

The only barrier to successful application of the reaction to fragment coupling is the necessity for mild, facile removal of the aldehyde-isonitrile moiety. Several approaches to this dilemma have been investigated via simple model reactions. The isonitrile is usually important only in solubility considerations, but such couplings utilizing cyclohexylisocyanide proceed as much as ten times faster than couplings using t-butylisocyanide.[26] No study has been published which gives a definitive reason for this. Cleavability of 2 depends only on the choice of the aldehyde component. Products of nearly 100% optical purity were commonly obtained from model reactions such as those shown in Table 1.[4,24] These reactions appear to work best in methanol at low temperatures.[4,23] 2-Nitro-benzaldehyde gives acceptable yields (65-70%) and allows cleavage by photolysis at 350 nm (60-80%). Electron donating counterparts, such as 2,4 dimethoxybenzaldehyde give poor yields for both the reaction and subsequent cleavage with anhydrous acid. 4-Pyridinecarboxaldehyde used in the synthesis of a dipeptide gave a 60% yield in the condensation step and quantitative cleavage under controlled potential. Further studies on this method are in order. Some other aldehydes were investigated, but the most promising of all so far is 1-BOC-3-formylindole (11). The H-bond adduct of TFA and 12 has a high tendency towards fragmentation due to the stability of the resulting carbonium ion.[3] Using TFA for this cleavage is sometimes desirable, since TFA is often the reagent of choice for deprotection as well. Ugi Reactions with this aldehyde (Scheme VIII) give yields ≧60% and the adduct is cleaved mildly with cold TFA in trifluoroethanol (70-75%).[23,4]

Scheme VIII. (BOC= $\overset{\displaystyle O}{\overset{\|}{C}}$ $OC(CH_3)_3$)

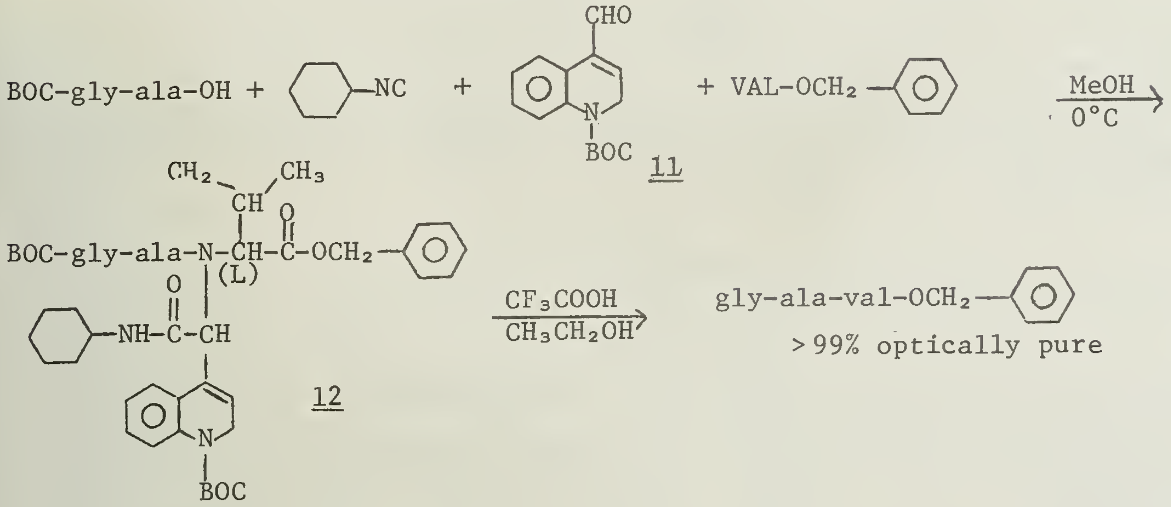
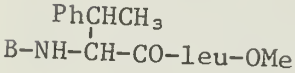

BOC-gly-ala-OH
NC
CHO
N
BOC
11
VAL-OCH₂
MeOH
0°C
CH₂
CH₃
CH
BOC-gly-ala-N-CH-C-OCH₂
(L)
NH-C-CH
12
CF₃COOH
CH₃CH₂OH
gly-ala-val-OCH₂
>99% optically pure

Table 1

acid	amine	aldehyde	% yield adduct	% cleavage	overall % yield
pht-gly-OH	H-gly-Otbu	O-nitrobenzaldehyde	67	61(hν)	41
"	"	2,4-dimethoxybenzaldehyde	34	38(HF)	13
"	"	4-pyridinecarboxaldehyde	60	100 (electrolysis)	60
"	"				
"	"	11	53	74(TFA)	39
"					
"	H-gly-OMe	11	56	70(TFA)	39
"					
"	H-gly-Otbu	3-formylindole	45	81(TFA)	36
"	H-gly-OMe	3-formylindole	35	79(TFA)	28
$ph-CH_2COOH$	$ph-CH_2NH_2$	2,4-dimethoxybenzaldehyde	75	38(TFA)	28
"	"	3-formylindole	62	70(TFA)	43
"	"	Ferrocenecarboxaldehyde	77	49(TFA)	38
"	"	N-methyl-2-pyrrolecarboxaldehyde	68	53(TFA)	36
"	"	O-nitrobenzaldehyde	72	65(hν)	47
Z-gly-ala-OH	H-leu-gly-Ot-bu	O-nitrobenzaldehyde	71	78(hν)	55
"	"	2,4-dimethoxybenzaldehyde	75	10(TFA)	8

Tables 1 and 2 summarize the results of some model reactions of this type with respect to yield and optical purity of the products.[4,5,27]

Table 2

product	mode of synthesis	aldehyde	% racemization*
 $\overset{\mathrm{PhCHCH_3}}{\mathrm{B\text{-}NH\text{-}\underset{}{CH}\text{-}CO\text{-}leu\text{-}OMe}}$	DCCD-HOSU	-----	10-11%
"	mixed anhydride	-----	96-100%
"	4CC		12%
"	4CC	$Cl_3CH=CH-CHO$	0.25%
N-TFA-VAL-gly-OEt	4CC	3-formylindole	0-1%
N-TFA-phe-gly-OEt	4CC	"	0-1%
N-formyl-VAL-gly-OEt	4CC	"	0-1%

*of aa unit that must normally be activated.

Recently, Ugi and coworkers have developed a new class of aldehydes that may prove even more efficient.[26,27] 8-Halogenated butenals, such as 13, form adducts 2 that are easily cleaved by supernucleophiles such as Co^I-phthalocyanine anion. Syntheses with model compounds have shown that good yields are obtained with practically no racemization. 13 is obtained via Wittig reaction of chloral with 2-oxoethylidenetriphenylphosphorane.[28] This class of aldehydes should give better overall yields and allow cleavage of the adduct without effect on other protecting groups.

$Cl_3C-CH=CH-CHO$

13

Little exploration of this technique beyond the realm of simple model reactions has been reported, a notable exception being the recent synthesis of some cyclic peptide derivatives by Immer, et al.[25]

Other Applications of the Ugi Reaction. Many other acids and amines can be used in the condensation.[2,14] Acids such as HNCO, HNCS, HN_3, $H_2S_2O_3$, H_2Se, and H_2O give intermediates which rearrange in a variety of ways. In the cases of H_2O, H_2Se, and $H_2S_2O_3$, the intermediate initial adduct tautomerizes to give the amide, selenamide, or thioamide product. HN_3 causes cyclization of the initial adduct to give a tetrazole. These reactions take place regardless of whether a primary or secondary amine is used. HNCO and HNCS provide novel routes to some interesting heterocyclic compounds when condensed with primary amines.[14] Hydroxylamines and hydrazines have been employed with some success as amine components in Ugi Reactions. The first preparation of N-aminopeptides was achieved by the use of hydrazines as the amino components in Ugi Reactions.[29] β-lactams are accessible through intramolecular Ugi Reactions.[30]

Conclusions. Moderate success has been achieved in dealing with the problems inherent in this approach to peptide chemistry. Progress is continuing,[26] but competitiveness with other methods of peptide synthesis has not attained a level of superiority necessary to bring the Ugi Reaction into common usage in this area. Nevertheless, these studies have already paid dividends in the fields of isonitrile chemistry, ferrocene chemistry, supernucleophiles, and asymmetric synthesis, which would seem to justify further investigations.

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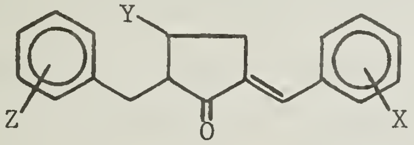
SOLID STATE ORGANIC PHOTOCYCLIZATIONS

Reported by Barbara Murray November 17, 1980

Major advances have been made recently in solid state chemistry enabling chemists to offer explanations for experimental observations previously unexplainable.[1,2] Using this knowledge, attempts at "crystal engineering" are being made, with hopes of forcing molecules into space groups conductive to a specific reactivity.[3]

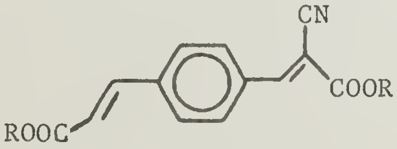
Two important concepts in solid state chemistry are topotaxy and topochemical control. Topotaxy means that the product has a definite orientation with respect to the starting material,[4] while topochemical control means that reactions in crystals proceed with a minimum of atomic and molecular movement.[5] In the solid state the intrinsic reactivity of a molecule can be of secondary importance to topochemical considerations such as space group or the distance between molecules.[6] Solid state reactions may proceed either by a "homogenous" mechanism in which there is a solid solution formed, or by a "heterogeneous" mechanism in which there is no mixing of product and starting material.[7]

One type of solid state reaction that has proved useful both synthetically and mechanistically is photocyclizations such as [2+2] and [4+4] dimerizations.[8-13] The crystal structure of the monomer is crucial: The double bonds involved must be between 3.6 and 4.1 Å apart[14] and parallel in order for the reaction to occur. The stereochemistry of the photodimer is determined by the geometry of the overlapped molecules.[5] Recently Jones and Thomas have studied the photoreactivity of 2-benzyl-5-benzylidenecyclopentanones[3] (1). They have tried to determine factors needed for crystal engineering and have monitored a single-crystal → single-crystal photodimerization.[15]



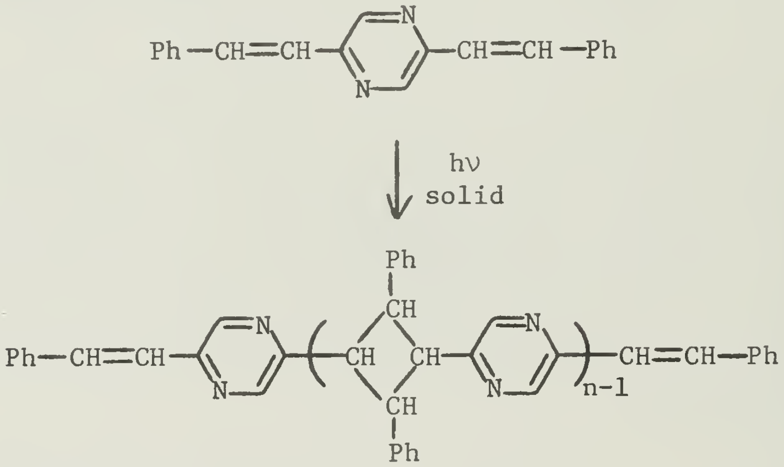
1

Using solid state chemistry it is possible to achieve absolute asymmetric syntheses, making chiral products from achiral precursors[6] because molecules that are achiral in solution can crystallize in chiral crystals.[16] Several optically active photodimers have been synthesized in the solid state from achiral monomers.[17-22] Addadi and Lahav have used the monomer (2) in the first solid state asymmetric synthesis with quantitative diastereomeric yield.[20]



2

It is possible to do photopolymerizations in the solid state which do not occur in solution and which often yield crystalline polymers of extended chains.[23–27] Although solution polymerizations are often amorphous, single-crystal → single-crystal polymerizations are possible in the solid state.[15] An example of a solid state photopolymerization is shown in Eq. 1.[4]



(1)

As more of the factors involved in solid state reactions become known, it should be possible to control the conditions to achieve a particular reaction result. In fact, solid state reactions which do away with solvent complications may soon become standard techniques for organic chemists.

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INTERFERONS; STRUCTURES AND TECHNOLOGIES

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Introduction. The primary structures of interferon (IFN) proteins determined so far are not unusual. They are straight chain proteins with no modifications at the amino or carboxyl termini, some may be glycoproteins. IFNs are an interesting study in structure determinations because of their unique circumstances. Their low cellular concentrations and difficulty of purification assures minute sample sizes. Media attention as "an ideal cancer drug"[1] and money ($150 million by pharmaceutical companies, $9 million by the National Cancer Institute and $3.8 million by the American Cancer Society)[1] have kept IFN at the frontier of technology. This seminar will examine IFN structural work and some of its associated technologies.

In 1957 Isaacs and Lindenmann[2] reported the discovery of a substance responsible for the phenomenon known as viral interference. They found that when heat-inactivated virus was incubated with a cell culture, the culture exhibited a resistance to a challenge virus. Furthermore, when the medium was filtered free of virus and cells and then used to culture new cells, they too were protected.

There are currently three classes of IFNs recognized based upon their antigenic specificities (α, β, γ).[3] The nomenclature defines the species (IFNs are species specific) and the class of IFN (e.g., Hu IFN-α1 would be an IFN from a human source belonging to the α class). In addition, the cell type is sometimes given.

The largest source of IFN is from induction of cell cultures, the form of IFN produced being dependent on cell type and inducer type.[4] Recombinant genetics has produced several lines of E. coli, producing both Hu IFN-α[5] and Hu IFN-β,[6] and will soon be a major supplier of IFNs.

The most common assay for IFN is based upon the cytopathic effect and relies upon the adsorption of a cellular dye by living cells.[7] A unit of IFN is the dilution required to inhibit cell destruction by one-half in the assay.

A wide variety of purification schemes have been utilized with IFNs. Each class of IFN is amenable to different purification schemes. Some of the techniques employed include high pressure liquid chromatography,[4d] molecular size exclusion chromatography,[8,4h] electrophoresis,[9] antibody affinity chromatography,[10] polynucleotide chromatography,[10c,11] zinc chelate affinity chromatography,[12] lectin and hydrophobic chromatography.[13] Most overall yields range from five to fifteen percent with activities of 10^8 to 10^9 units/mg.

IFNs as Glycoproteins. IFNs were recognized early as being or containing protein, from their destruction by proteolytic, but not other enzymes.[14] Studies also showed it to be of heterogeneous charge by electrophoresis, isoelectric focusing and ion exchange chromatography.[14] This kind of heterogeneity is often observed with glycoproteins, which contain variable amounts of terminal (sialic acid → galactose →) moieties. Each sialic acid adds a negative charge and hence its presence or absence contributes to the heterogeneity. Schonne et al.[15] showed that neuraminidase decreased the heterogeneity of crude rabbit IFN on isoelectric focusing, without destroying its activity. Dorner et al.[16]

showed that the heterogeneity returned upon reincorporation of CMP-sialic acid.

The production of IFNs in the presence of inhibitors of glycosidation has been investigated.[17] Fujisawa et al. induced Mu IFN production in the presence of tunicamycin, ^{35}S-methionine, and ^{3}H-glucosamine. He found that the IFN shifted to a lower molecular weight and had a higher $^{35}S/^{3}H$ ratio than controls.

The only indications of specific sugars in purified IFN samples were observed by Tan et al.[18] who found evidence of galactosamine or mannosamine in Hu IFN-β and by Cabrer et al.[4i] who identified glucosamine in Mu IFN-α and -β. Both findings were the result of amino acid analysis.

IFN Proteins. Amino acid analysis of IFN's has revealed similar compositions, for IFN-αs and IFN-βs and some differences. Table 1 compares the various amino acid compositions determined and inferred from various studies. Rubinstein et al.[4d] were the first to report an amino acid analysis (Table 1) on a highly purified interferon (2-4 x 10^8 units/mg). They found Hu IFN-α from leukocytes to be rich in leucine, lysine, glutamic acid/glutamine and aspartic acid/asparagine. This has since been found to be a property of all IFNs. It also contained very little tryptophan. Based upon a minimum cystine content, the protein was calculated to have a molecular weight of 18,000 daltons. Zoon et al.[19] reported an amino acid analysis of Hu IFN-α from lymphoblasts with a molecular weight of 18,500 daltons and an activity of 2.5 x 10^8 units/mg, based upon the amino acid analysis (Table 1). Attempts to identify the amino terminus by dansylation failed, due to contaminating peptides.

Tan et al.[18] were the first to purify Hu IFN-β (5 x 10^8 units/mg) with respect to both size (20,000 daltons) and charge. The results are similar to those for Hu IFN-α but with some discrepancies. They incorrectly found the peptide to be void of methionine (resistant to cyanogen bromide) and tryptophan (hydrolysis in 4 N methane sulfonic acid, 18 h, 25°C). Knight et al.[20] have also published an amino acid analysis for Hu IFN-β (2-8 x 10^8 units/mg).

Cabrer et al.[4i] isolated a Mu IFN-α (20,000 daltons) and two Mu IFN-βs (33,000 daltons and 26,000 daltons) from murine Ehrlich ascites tumor cells. Two dimensional thin layer chromatography of the tryptic digest of the proteins revealed the similar nature of the Mu IFN-βs and distinct differences in the Mu IFN-α. Amino acid analysis also showed the Mu IFN-βs to be similar while Mu IFN-α was slightly different (Table 1). A mixture of the Mu IFN-βs gave only dansylisoleucine, while Mu IFN-α gave a mixture of dansylisoleucine and bis-dansyllysine upon dansylation. When a mixture of the Mu IFN-βs was subjected to dansyl-Edman degradation, the second and third amino acids were determined as lysine and tyrosine, respectively. Treatment of the mixture with carboxypeptidase A followed by ^{14}C-dansylation revealed phenylalanine, leucine, and lesser amounts of lysine, indicating the partial sequence Ile-Lys-Tyr---[Lys, Phe, Leu].

Automated amino acid sequencing was first successfully used on IFNs by Hunkapiller and Hood.[21] The very limited amounts of IFN available made sequencing by conventional methods impossible.

Hunkapiller and Hood have developed sequencing techniques 10,000 times as sensitive as Edman and Begg's original sequenator.[22] They have sequenced the amino terminal of five different IFNs: Hu IFN-α (Zoon et al.[23]), Hu IFN-β (Knight et al.[20]), Mu IFN-α and two Mu IFN-βs (Taira et al.[24]).

The major component of Hu IFN-α from lymphoblasts produced and purified by Zoon et al. was subjected to six sequencings at 20-500 pico moles per run. The sequence of the first 20 amino terminal amino acids was established and later expanded to 35 amino acids (Figure 2).

Hu IFN-β produced and purified by Knight et al. was sequenced in three runs, 0.4 to 2 μg samples, to give 13 amino terminal amino acids (Figure 2). A high yield in the first cycle of Met-PTH (60-100%) and the lack of unblocked minor peptide sequences (< 5%) confirmed the homogeneity of the sample. Repetitive cycle yields were 92-95%. There were no similarities in the Hu IFN-α and Hu IFN-β amino terminal sequences.

When the three mouse IFNs produced and purified by Taira et al. were sequenced, the two Mu IFN-βs gave identical sequences for the first 24 amino terminal amino acids with the exception of residue 17 which was not identified (Figure 2). The first 20 amino terminal residues revealed by protein sequencing of Mu IFN-α showed little homogeneity with Mu IFN-βs. It was however noted that Mu IFN-βs have three of thirteen amino terminal amino acids in common with Hu IFN-β. Mu IFN-α shows correlation with 13 out of 20 of the amino terminal amino acids of Hu IFN-α.

Nucleotide Sequencing. Recently the entire amino acid sequence of several IFNs has been implied by sequencing of various genes coding for IFN proteins.

There are two main schemes for sequencing DNA. They are the chain terminating[25] and the Maxam-Gilbert[26] methods. Both rely on incorporation of ^{32}P into all possible fragments of the DNA containing the 5' end and a specific 3' terminal nucleotide, followed by resolution of these fragments by size on denaturing acrylamide gel. Therefore, three specific terminators or three specific cleavages are needed. As a check, most work is done with four terminators or four cleavages.

The chain-terminating method relies upon incorporation of the 2',3'-dideoxytriphosphate analogs of the four nucleotides into the growing nucleotide sequence along with a ^{32}P-nucleotide.

The Maxam-Gilbert method relies upon chemical cleavage of terminally labeled DNA at a specific nucleotide. The purine-specific reaction is methylation with dimethylsulfate producing 7-methylguanine and 3-methyladenine[27] in a 5:1 ratio.[28] The glycosidic linkage of a methylated purine is unstable upon heating at pH 7, the rate of liberation of 3-methyladenine being greater than 7-methylguanine.[27] The resulting nick in the DNA can be hydrolysed with 0.1 M NaOH at 90°C.[26] Because guanine methylates five times faster than adenine complete hydrolysis of the bases followed by hydrolysis of the sugars from the phosphates in alkali gives a dark band for guanine and a light one for adenine. However, gentle treatment of the methylated DNA in dilute acid to preferentially remove the

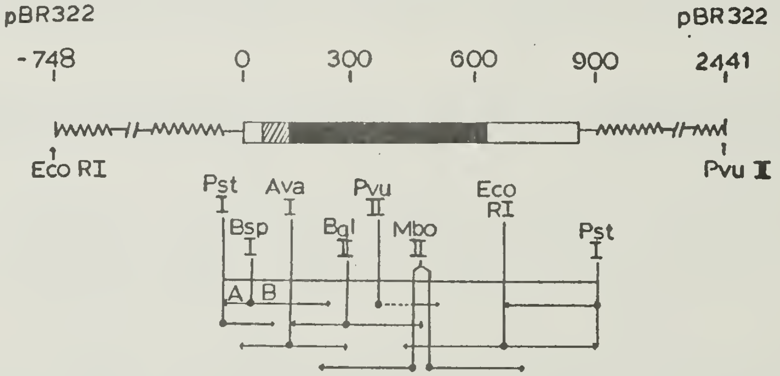
3-methyladenines, followed by cleavage with alkali, gives dark bands for adenine and light bands for guanine.

Pyrimidine bases are attacked by hydrazine which cleaves the base and leaves ribosylhydrazone.[29] The DNA is then cleaved by displacement of the products of the hydrazine reaction from the sugar by piperidine, which also catalyzes the β-elimination of phosphates. This gives rise to bands from cytosine and thymine of similar intensity. The reaction of hydrazine with thymine can be preferentially suppressed by 2 M sodium chloride, giving rise to bands only from cytosine.

Mantei *et al.*[30,5a] combined the cDNA coding for Hu IFN-α from reverse transcription of isolated Hu IFN-α mRNA with the pBR322 plasmid. They have cloned it in *E. coli* and sequenced the 910 base pair (bp) insert.

The plasmid was cleaved at the Pst I site and elongated with dG residues. The dC elongated Hu IFN-α cDNA was hybridized with the plasmid and patched with DNA polymerase, then sealed with DNA ligase. A restriction site map of the insert was generated (Figure 1) by the Smith-Birnstiel method,[31] which is similar to the Maxam-Gilbert method except that partial digestion by various restriction enzymes replaces specific base cleavages. As an example, complete cleavage of the plasmid with Pst I, labeling the fragments with ^{32}P and separating them by electrophoresis gives the 910 bp insert. Cleavage with a second restriction enzyme with only one site, Bgl II, results in isolation of two double-strand fragments with one labeled 5' end. These are partially digested separately by a variety of restriction enzymes and resolved by electrophoresis. The sequential restriction sites along the fragment are then read off the gel.

Figure 1[a]



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[a] Strategy for the determination of the nucleotide sequence of Hu IFN-α DNA. The filled circles represent labeled 5' termini, the solid arrows indicate the sequences read off the fragments. The dashed lines represent regions not read off a particular fragment. Upper map: numbers indicate bp; black segment, interferon coding sequences; hatched segment, putative signal sequence; white segment, non-coding region; straight lines, next to rectangle, homopolymeric dG:dC flanking regions; wavy lines, pBR322.

Each fragment (Figure 1) was isolated and sequenced, thus giving pieces small enough to sequence, overlap to establish continuity, and by sequencing both strands, an internal check.

A typical isolation (fragments A and B) involves cleavage of the plasmid with Bsp I and isolation of the fragments by electrophoresis (a 232 bp section for A and a 949 bp section for B). These are labeled at the 5' ends and cleaved with Pst I, giving upon separation a 5' labeled Bsp I - Pst I 83 bp section for A and a 5' labeled Bsp I - Pst I 827 bp section for B.

The nucleotide sequence has 23 dG residues in the homopolymeric flanking region. An ATG initiation codon at -69 bp codes for a 23 residue signal peptide, or a second in-phase ATG triplet at -45 bp codes for a 15 residue signal peptide. The mature IFN protein was predicted by comparison to Zoon's amino terminal sequence. The mature protein is 166 residues long and transcription terminates with a TAA codon. The untranslated 3' end is 242 nucleotides long and has a high A + T content. The AATAAA sequence appears 21 bps upstream from the poly A tail. The mature IFN protein coded for has a calculated molecular weight of 19,388 daltons compared to 25,000 to 21,000 for glycosylated Hu IFN-α and 21,800 to 15,000 for nonglycosylated Hu IFN-α by electrophoresis.

In the first 35 amino terminal amino acids there are nine differences from Zoon's Hu IFN-α. Each one could arise from a single base change. The magnitude of these differences suggests that these are not multiple alleles but are different genes. Mantei looked through his clones for further evidence of this and found a clone with a different restriction pattern. The structure of this gene was presented by Streuli et al.[32] (Figure 2). They proposed the existence of at least three Hu IFN-α genes. This was based on the fact that Mantei's Hu IFN-α (Hu IFN-α1) differs from Zoon's Hu IFN-α (Hu IFN-α3) in nine of thirty-five amino terminal amino acids and the newly sequenced Hu IFN-α (Hu IFN-α2) in 20% of the nucleotides (10% in the coding region) and 17% of the amino acid residues. Hu IFN-α2 differs from Hu IFN-α3 in five of the first thirty-five residues. Hu IFN-α2 is only 165 amino acids long compared to 166 for Hu IFN-α1. Hu IFN-α1 is 10 to 20 times as active on bovine as on human cells while Hu IFN-α2 is twice as active on human as on bovine cells.

Goeddel et al.[5b] independently proposed the same structure for Hu IFN-α2 except for one base at position 68 which changes an AGA codon for arginine to an AAA codon for lysine.

More recently, Nagata et al.[5c] have reported the existence of at least eight distinct chromosomal genes for Hu IFN-α. It is hoped that the genes may code for specific activity and the effects so far ascribed to Hu IFN-α may be due to a mixture of different effects of all the Hu IFN-αs.

Allen and Fantes, using Hu IFN-α produced on a large scale (4 mg for this study alone compared to 2.4 μg total for three amino terminal sequences by Hood and Hunkapiller[21]), separated it into two fractions on sephadex G-75 (A, B). Two dimensional chromatography of the tryptic digest of the performic acid oxidized fractions showed A to be almost homogeneous, in contrast to B. The proteins and some of

Table 1. Amino Acid Compositions Residues/166 Residues[a]

	IFN-αs				IFN-βs			
Amino Acid	A	B	C	D	E	F	G	H
Asx	15.7	15.0	15.5	17	18.9	18.6	15.2	17
Thr	7.7	8.1	10.2	9	7.7	6.7	12.5	6
Ser	8.3	10.7	10.1	13	12.5	10.3	7.8	9
Glx	24.8	27.4	26.1	25	26.6	26.5	28.8	24
Pro	6.5	11.0	6.3	6	5.0	2.7	2.0	1
Gly	5.7	10.7	6.9	3	ND	7.7	4.2	6
Ala	8.5	11.1	10.7	10	9.7	9.8	7.5	6
Cys	3.4	1.8	ND	5	7.8	1.7	ND	3
Val	8.0	7.7	7.6	6	8.2	5.9	7.4	5
Met	4.0	3.0	4.6	6	0.3	2.8	6.3	4
Ile	9.2	7.0	5.7	7	8.7	8.8	6.8	11
Leu	22.5	18.0	18.3	22	25.6	20.0	20.8	25
Tyr	5.3	3.9	5.3	4	4.0	7.4	8.2	10
Phe	9.4	7.2	6.5	8	6.8	9.2	7.8	9
His	3.4	4.4	4.4	3	4.2	4.8	2.2	5
Lys	12.0	10.5	17.4	8	11.2	11.4	14.2	11
Arg	7.5	9.7	10.5	12	8.7	10.7	13.3	11
Trp	0.7	0.6	ND	2	0.0	1.0	ND	3

[a] A, Rubinstein *et al.*, leukocyte Hu IFN-α; B, Zoon *et al.*, lymphoblast, Hu IFN-α; C, Cabrer *et al.*, Mu IFN-α; D, Mantei *et al.*, Hu IFN-α1; E, Tan *et al.*, fibroblast Hu IFN-β; F, Knight *et al.*, fibroblast Hu IFN-β; G, Cabrer *et al.*, Mu IFN-β; H, Taniguchi *et al.*, Hu IFN-β; ND, not determined.

the peptides resulting from tryptic and chymotryptic cleavages have been sequenced by the dansyl-Edman method (Figure 2). Some of the cycles in A were found to consist of two amino acids indicating two very similar homologs, while some fragments from B could be separated into at least three homologous series.

Because of gaps in the sequences and because of the lack of overlap in many of the cleavages, little ordering of the peptides could be made. However, the inferred protein sequence derived for other Hu IFN-αs could be used as a pattern to piece together the fragments. From this it was clear that A probably is or contains Hu IFN-α2 differing only in positions 83 (Asp/Lys) and 87 (Pro/Glu), while B resembles Hu IFN-α1 differing in positions 60 (Met/Leu) and 64 (Thr/Ile). Other than Zoon's[23] amino terminal sequence, Allen's fragments give the first direct evidence supporting the DNA inferred Hu IFN-α amino acid sequences. Especially important is the C-terminal region which shows no modifications.

Figure 2.[a]

Amino Acid Sequences

```
A  (M A S P P A L L M V L V V L S C K R S C S L C)C D L P E T 006
B                                                 C D L P E T 006
                                                          Q
C              (L L V A L L V L S C K S S C S V C)C D L P Q T 006
D                                                 C D L P Q T 006
E                                                 R D L P Q T 006
F                                                 A D L P Q T 006
Com             L L     L   V L S C K S S C S   C)  D L P   T
a                                           M S Y N L L G F L 009
b(M T H K C L L Q I A L L L C F S T T A L S)M S Y N L L C F L 009
c                                           I N Y K Q L Q L Q 009
com                                             Y     L
---------------------------------------------------------------
                                    R
A   H S L D N R R T L M L L A Q M - S R I S P S S C L M D R H 034
B   H S L D N R R T L M L L A Q M - S R I S L P S C L K D R H 034
          D       A   I             C       P S       M   H R
C   H S L G S R R T L M L L A Q M - R R I S L F S C L K D R H 034
D   H S L G S R R T L M L L A Z M - R R I S L F S C L K D R H 034
                                                            R
E   H S L C N E R A L I L L A Q M - G R I S L F S C L K D R H D34
F   Y H L G N K C A L K V L A Q                               020
Com                 L     L A Q M     R I S     S C L   D
a   Q R S S                                                   013
b   Q R S S N F Q C Q K L L W C L H G R - - L E Y C L K D R M 036
c   E R T N I R K   Q E L L E Q L                             024
com R               Q   L L   Q L
---------------------------------------------------------------
A   D F C F P Q E R F D C N Q F Q K A P A I S V L H E L I Q Q 063
B   D F D F P Q R E F D G N Q F Q K A P A I S V L H R M I Q Q 063
        R I                         T Q                 L
C   D F G F P Q E R F   G N Q F Q K A E T I P V L H R M I Q Q 062
D   D F C F P Q E R F   G N Q F Q K A E A I S V L H E M I Q Q 062
                                        T   P
Com D F     P Q E E F   G N Q F Q K       I   V L H E M   Q Q
b   N F D I P E E I K Q L Q Q F Q K E D A A L T I Y E M L Q N 065
---------------------------------------------------------------
A   I F N L F T T K D S S A A W D E D L L D K F C T E L Y Q Q 092
B   T F R L F T T K D S S A A M D Z D L L D   F C T E L Y Q Q 092
              S   Z         T     D T           S
C   I F R L F S T K D S S A A M D E T L L D K F Y T R L Y Q Q 091
D   I F N L F S T K D S S A A   D E T L L D D F Y T P L Y     091
                        Z
Com   F N L F   T   D S   A   N D     L L D   F   T   L Y Q Q
b   I F A I F R Q D S S S T G W N E T I V E N L L A N V Y H Q 094
---------------------------------------------------------------
A   L N D L E A C V M Q R E R V D E T P L M N A D S I L A V K 121
B   L N D L E A C V M         V D E T P L M N A D S I L A V K 121
                    L                                       R
C   L N D L R A C V I Q C V G V T E T P L M K A D S I L A V R 120
D                                             E D S I L A V R 120
Com L N D L E A C V   Q       V   E T P L M N   D S I L A V
b   I N H L K T V L E E K L E K E D F T R G K L M S S L H L K 123
---------------------------------------------------------------
A   K Y F R R I T L Y L T E K K Y S P C A M E V V R A E I M R 150
B   K Y F R R I T L Y L T R K K Y S P C A M E V V R A E I M R 150
          Q
C   K Y F Q R I T L Y L K R K K Y S P C A M E V V R A E I M R 149
D   K Y F Q R I T L Y L K R K K Y S P C A M   V V R A E I M R 149
Com K Y F   R I T L Y L   E K K Y S P C A M E V V R A E I M R
b   R Y Y G R I L H Y L K A K E Y S H C A W T I V R V E I L R 152
---------------------------------------------------------------
A   R L S L S T N L Q E R L R R K E                           166
B   S L E L S T N L Q R R L R R K R                           166
      F   F           K       S   R
C   R F S L R T N L Q R S L R R K R                           165
D   R F S L S T N L Q R S L R R K R                           165
Com R   S   S T N L Q     L R   K
b   N F Y F I N R L T G Y L R N                               166
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A Hu IFN-β gene has been sequenced by Taniguchi et al.[34,6a,c] (Figure 2) who recombined cDNA synthesized in vitro by reverse transcription of fibroblast Hu IFN-β mRNA. The plasmid cDNA was isolated and fragments containing the cDNA mapped. The fragments were sequenced by the Maxam-Gilbert method. There are at least six codons before the first in-phase AUG codon. By comparison to Knight's[20] amino terminal sequence, the first amino acid of the mature protein was identified and it was preceded by a 21-residue signal peptide. The mature protein was 166 residues long and transcription terminated by a TGA codon. The molecular weight calculated for the peptide would be 20,040 daltons compared to 26,000 to 20,000 daltons for glycosylated and 16,000 daltons for nonglycosylated Hu IFN-β by electrophoresis.

Dermyck et al.[6b] independently determined the identical nucleotide sequence from an *E. coli* clone in which they had implanted the Hu IFN-β gene. They also noted that N-glycosidic linkage is possible at the -Asp-Glu-Thr- sequence (position 80).

[a] Comparison of IFN proteins: A, Hu IFN-α1 (Mantei et al.); B, Hu IFN-αB (Allen et al.); C, Hu IFN-α2 (Streuli et al.); D, Hu IFN-αA (Allen et al.); E, Hu IFN-α3 (Zoon et al.); F, Mu IFN-α (Taira et al.); Com, Common amino acids in all IFN-αs; a, Hu IFN-β (Knight et al.); b, Hu IFN-β (Taniguchi et al.); Mu IFN-β (Taira et al.); and com, common amino acids in all IFN-βs. The sequences are written in one letter nomenclature according to the IUPAC-IUB Commission on Biochemistry Nomenclature: A, alanine, C, cysteine, D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, pyroline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine; Z, Glx; B, Asx.

Conclusion. The two types of IFN genes sequenced to date (Hu IFN-αs and Hu IFN-βs) code for proteins with many differences: They are neutralized by different antibodies, their target cell specificities differ and their amino acid sequences differ.[32] However, a comparison of the nucleotide sequences of the coding regions shows an average homology of 45%. Rather than being random, specific regions of the DNA seem to account for the homology. On this basis and the degree of homology of human β-globin, α-globin and myoglobin (24% homology) and their calculated divergence of 500 to 1,000 million years (vertebrates develop) Taniguchi *et al.*[35] predict that all vertebrates will possess IFN-αs and -βs. This is evident in the case of Hu IFN-α, which has more in common with Mu IFN-β than Hu IFN-β, which in turn has more in common with Mu IFN-β than Hu IFN-α.

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THE INHIBITION OF THYMIDYLATE SYNTHETASE BY 5-SUBSTITUTED URIDINES

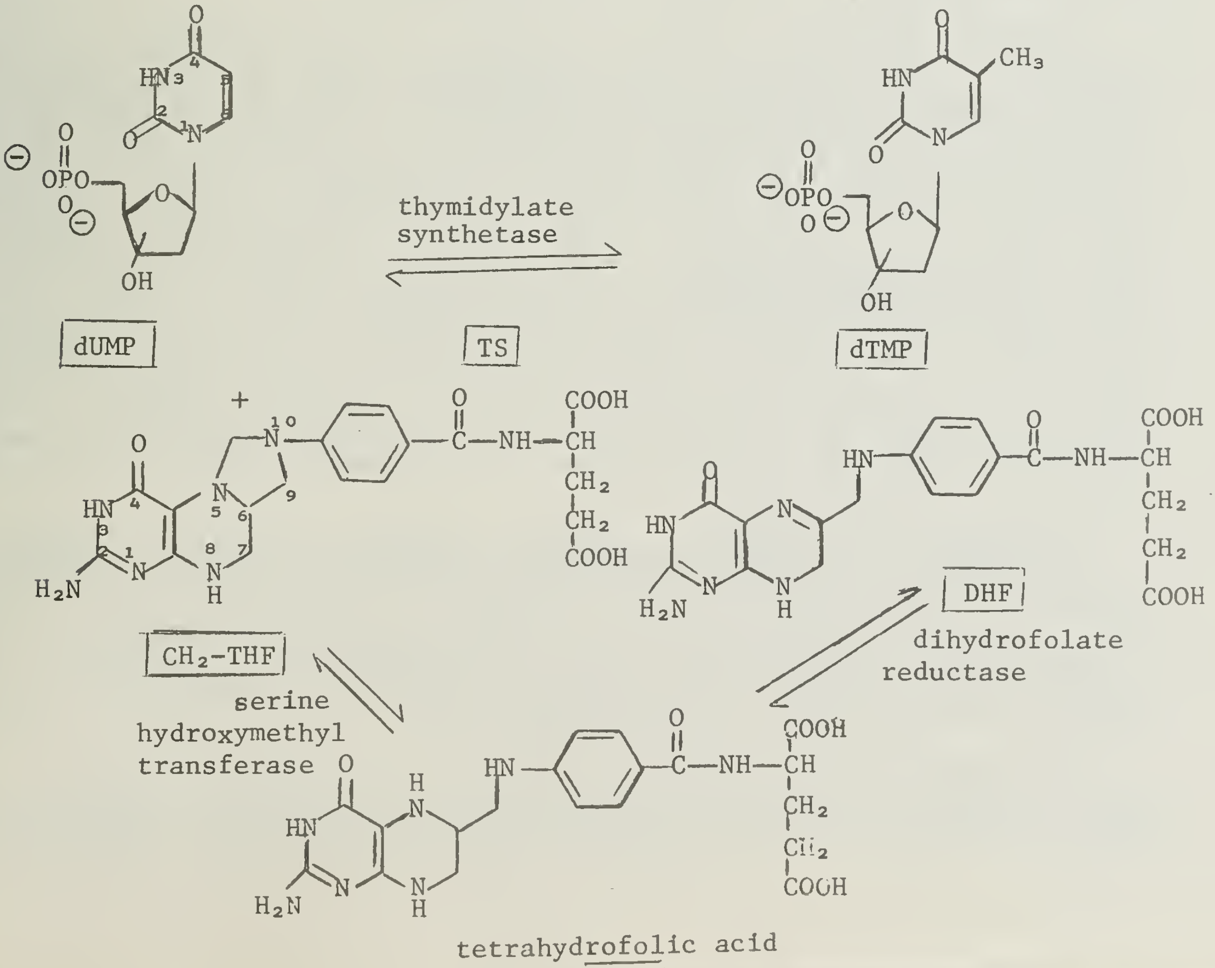
Reported by Marc d'Alarcao November 24, 1980

Introduction. The ability to selectively inhibit the growth of rapidly proliferating cells has been the goal of medical researchers for many years. It is clear that such an ability would have profound consequences in the treatment of neoplastic disease as well as certain bacterial and viral infections. One approach to this problem has been to try to block the ability of a cell to manufacture normal DNA. In this way those cells which are dividing rapidly, and consequently producing relatively large amounts of DNA, will be selectively damaged.

During the biosynthesis of DNA, ample supplies of the four DNA nucleotides must be maintained within the cell. Of these only 2'-deoxythymidine monophosphate (dTMP) is synthesized de novo for this process. The other three are readily available via enzymatic interconversions. The blocking of dTMP synthesis in vivo, therefore, will uniquely end normal DNA synthesis and result in "thymineless death."[1]

dTMP is synthesized in the cell by the enzyme thymidylate synthetase (TS) from 2'-deoxyuridine monophosphate (dUMP) by methyl transfer from a cofactor, N^5,N^{10}-methylene tetrahydrofolic acid (CH_2-THF). During the course of this reaction the cofactor not only undergoes a demethylation, but also an oxidation to dihydrofolic acid (DHF) and, therefore, must be regenerated by a two enzyme process before it can be reused in the thymidylate synthetase reaction. The overall scheme is illustrated in Figure 1.

Figure 1



An extensive research effort has been undertaken aimed at the inhibition of these enzymatic processes. For example, amethopterin[2] (methotrexate) and trimethoprim[2,3] are potent competitive inhibitors of dihydrofolate reductase and are currently finding clinical use as antileukemic and antibacterial agents, respectively. It is the purpose of this report to describe some recent approaches to the inhibition of thymidylate synthetase by dUMP analogues substituted in the 5-position, as well as to present highlights of the historical progress in the field.

Catalytic Mechanism. Several excellent discussions of the mechanism of catalysis for thymidylate synthetase have appeared.[4-7] Following is a description of the most widely accepted pathway (Fig. 2) from reactants to products, and some of the more persuasive arguments in support of this pathway.

There is little doubt that in productive catalysis the enzyme exhibits cooperative binding; TS binds CH_2-THF first (step 1, Fig. 2), then this binary, non-covalent complex accepts dUMP to form (step 2, Fig. 2) a ternary, non-covalent complex.[8] Step 3 in the sequence, however, has been subject to some debate. To support their hypothesis that attack by some TS nucleophile on the 6-position of the dUMP ring is necessary to activate the 5-position toward electrophiles, Santi and Brewer[9] performed an interesting model study. These workers subjected a series of uridines varying in the number and position of hydroxyl groups on their sugar moieties to sodium methoxide in deuterated methanol and monitored the incorporation of deuterium at the 5-position of the pyrimidine. They found that incorporation only occurred in those compounds which have a hydroxy group in a spacial disposition allowing them to add nucleophilically to the 5,6 double bond (Fig. 3). The conclusion which was drawn was that nucleophilic attack is an essential prerequisite to electrophilic substitution at the 5-position of these systems.

The most convincing evidence to date that nucleophilic addition to the 6-position of dUMP occurs in the TS reaction has come from studies with 5-fluoro-2'-deoxyuridine monophosphate (F-dUMP). This analogue when incubated with TS and CH_2-THF forms what is believed to be a covalent adduct with the enzyme.[10] If radiolabeled analogue ([6-^{3}H]-F-dUMP) and cofactor ([^{14}C]-CH_2-THF) are employed and the resulting complex is subjected to degradation by trypsin, both radioisotopes are found to remain bound to the same peptide fragment.[11] Additionally, slow dissociation of the complex is found to be first order and temperature dependence studies of the rate constant yield an activation barrier of E_a=29.0 Kcal/mol.[12] These data are consistent with the formation of a covalent, ternary complex such as [A] in Fig. 2. It is believed the F-dUMP enters the catalytic cycle in the same way as the natural substrate, proceeding through steps 1, 2, and 3 (Fig. 2), but cannot undergo step 4 due to lack of an abstractable proton at the 5-position. It is therefore trapped as the fluoro analogue of intermediate [A].

To further investigate this hypothesis, a mixture of [2-^{14}C]-F-dUMP and [6-^{3}H]-F-dUMP was incorporated into a complex with CH_2-THF and TS. The rate constants for dissociation of each radiolabeled species were obtained showing an isotope effect k_H/k_T=1.23.[12] This is equivalent to a k_H/k_D=1.15.[13] This secondary kinetic isotope effect is consistent with the decrease in coordination expected upon dissociation of intermediate [A].

The ^{19}F NMR spectrum has been observed for the F-dUMP-TS-(CH_2-THF) complex. A doublet of triplets is seen, believed to arise from coupling with the 6-proton as well as the two methylene bridge protons between F-dUMP and THF.[14]

Figure 2

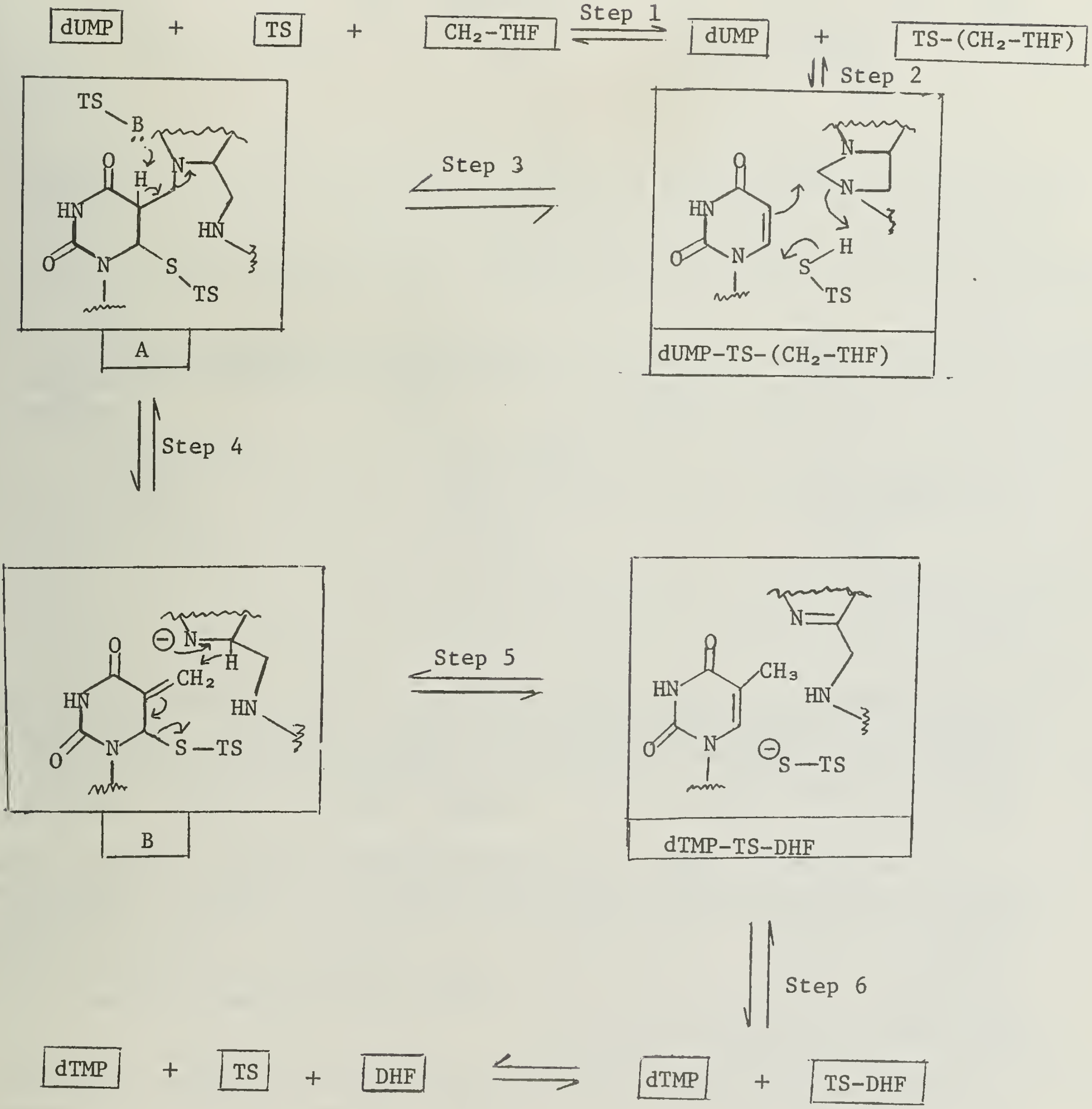
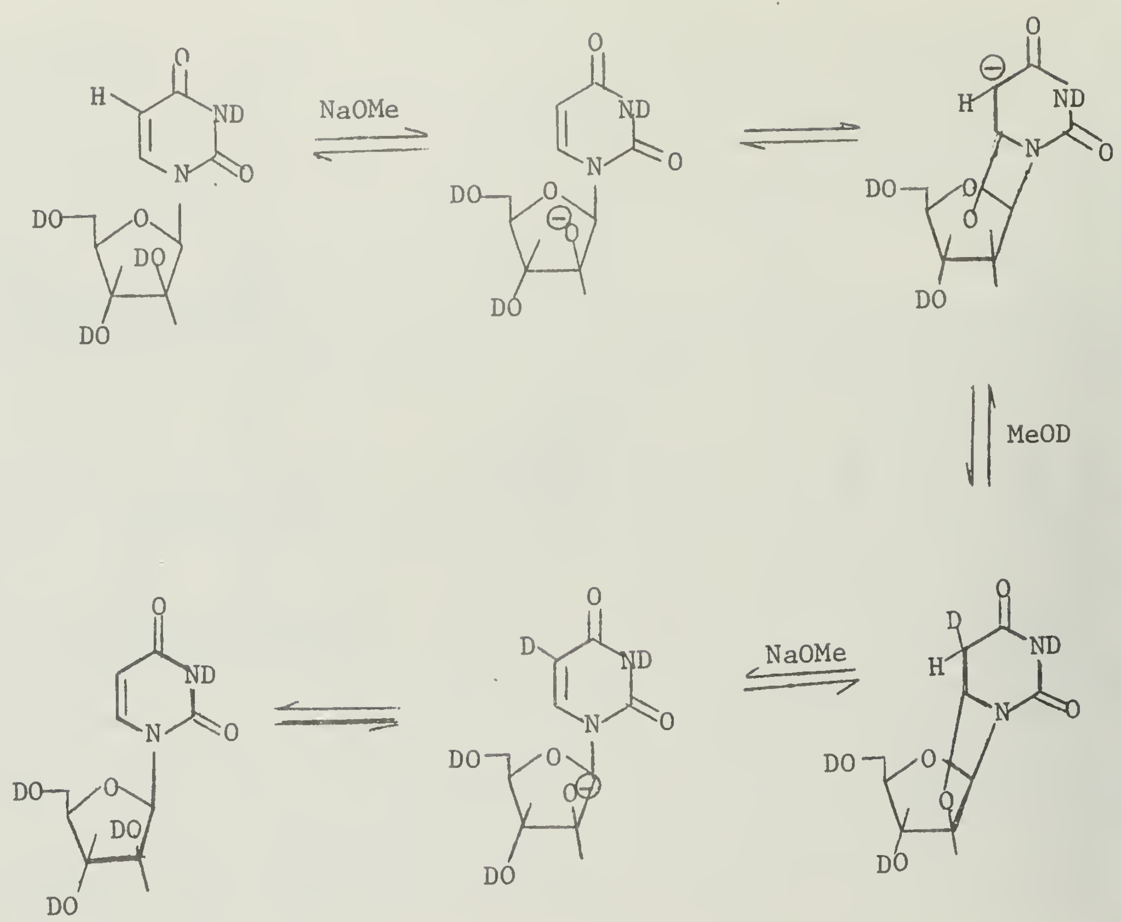

dUMP
+
TS
+
CH₂-THF
Step 1
dUMP
+
TS-(CH₂-THF)
Step 2
Step 3
A
dUMP-TS-(CH₂-THF)
Step 4
B
Step 5
dTMP-TS-DHF
Step 6
dTMP
+
TS
+
DHF
dTMP
+
TS-DHF

Figure 3

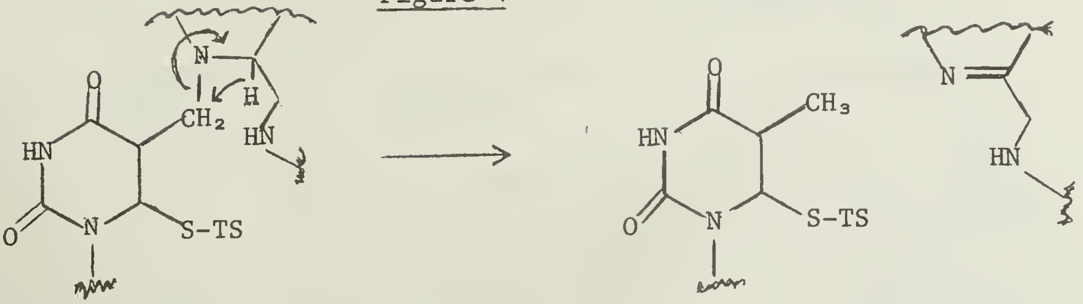


The possibility remains that in intermediate [A] the methylene bridge is bonded to N^{10} of THF rather than N^5 as depicted in Fig. 2. Though this possibility cannot at present be ruled out, Sommer and Santi[15] contend that the ultraviolet and fluorescence spectra of the complex (with F-dUMP) resemble those of 5-methyl tetrahydrofolic acid more than the 10-methyl derivative.

The question of which active site nucleophile is involved in the formation of intermediate [A] has also been answered by study of the F-dUMP covalent complex. When treated with Raney Nickel the complex rapidly releases both F-dUMP and cofactor.[11] This suggests the possibility of a sulfur nucleophile. Subsequent sequencing studies on the peptides derived from this complex strongly suggest that it is the -SH function of a cysteine residue in the active site which is the nucleophile.[16,17]

Unfortunately F-dUMP cannot be used to help elucidate the mechanism of steps after step 3 (Fig. 2), since it never reaches them. For this reason there is considerably more debate regarding these subsequent steps. For example, it has been suggested that step 4 may not actually involve a proton abstraction but first a 1,3 hydride shift from C-6 of THF to the bridge methylene (Fig. 4).[4] Pogolotti and Santi[18] favor the scheme illustrated in Fig. 2 on the basis of kinetic studies which they performed on the hydrolysis of 5-p-nitrophenoxyuracils in which there is strong evidence for [B]-type intermediates. Conclusions from this indirect evidence on the mechanism of TS catalysis is, of course, highly speculative.

Figure 4



That a hydrogen is transferred from C-6 of THF to the methyl group of dTMP at some point seems certain. If [6-^{3}H] labeled CH$_2$-THF is used as cofactor in the reaction, the resulting dTMP has exactly one ^{3}H and two ^{1}H in the methyl group.[4] An attempt has been made to measure an isotope effect in this case and preliminary results indicate that the magnitude of k_H/k_T is about of the order of a primary kinetic isotope effect in the rate determining step.[19]

The mechanism illustrated in Fig. 2, therefore, is consistent with all the available data. For this reason analysis of inhibition shall be based on that scheme.

Inhibition. One can envision three general modes of inhibition based on the mechanism illustrated in Fig. 2. These will be considered separately.

i) reversible, noncovalent inhibition

In this case the inhibitor competes with dUMP for the binding site on the enzyme. The degree of inhibition is based solely on the relative affinity of TS toward the two competing compounds. Santi has sought to establish some quantitative structure-activity relationships among 5-substituted pyrimidines[20] and he proposes the following minimal requirements on the dUMP analogue for efficient binding to TS:[21] a) 5'-phospho-2'-deoxyribosyl moiety, b) 2-keto function, c) 3-NH function, and d) a 4-substituent which doesn't tautomerically remove the 3-proton. Fortunately the 5-position substituent may vary considerably without precluding binding.

A number of workers have synthesized and tested pyrimidines on this basis.[20-28] A brief list of such compounds and their inhibitor constants is presented in Table 1. It should be noted that dTMP is a weak competitive inhibitor of TS.

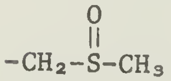
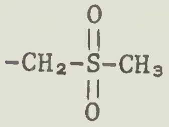
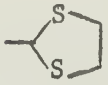
ii) reversible, covalent inhibition

Inhibitors of this type initially compete for the active site of the enzyme as in the previous case, but once bound they are subject to nucleophilic substitution at the C-6 position resulting in a relatively stable covalent complex. This complex can slowly dissociate to release unchanged inhibitor and enzyme.

F-dUMP is an inhibitor of this kind, and as mentioned earlier, the ternary F-dUMP-TS-(CH$_2$-THF) complex has been isolated.[10-17]

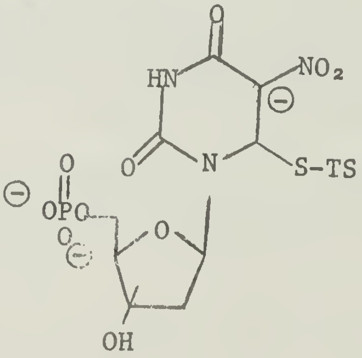
5-nitro-2'-deoxyuridine monophosphate (NO$_2$-dUMP) also exhibits this kind of inhibition. Initially it binds competitively with a Ki=0.029uM (L. Casei TS).[29] Upon incubation, however, NO$_2$-dUMP forms a covalent adduct which can slowly dissociate.[30] It is interesting that, unlike F-dUMP, this compound does

Table 1. Inhibitor constants for some 5-substituted dUMP's with thymidylate synthetase from L. Casei

5-substituent	Ki (uM)	reference
$-CN$	0.55	25
$-SH$	0.04	26
$-CH_2-S-CH_3$	2.40	27
 $-CH_2-\overset{\overset{O}{\|}}{S}-CH_3$	1.90	27
 $-CH_2-\underset{\underset{O}{\|}}{\overset{\overset{O}{\\|}}{S}}-CH_3$	2.20	27
$-CH_2OH$	8.30	20
$-CH_3$ (dTMP)	15.50	20
$-CH=N-OH$ (isomer mixture)	2.10	28
	0.67	28

not require the presence of CH_2-THF to form a stable covalent complex. This is interpreted[21] as resulting from the great stability of the anion which is formed upon nucleophilic addition to position 6 of the pyrimidine (Fig. 5).

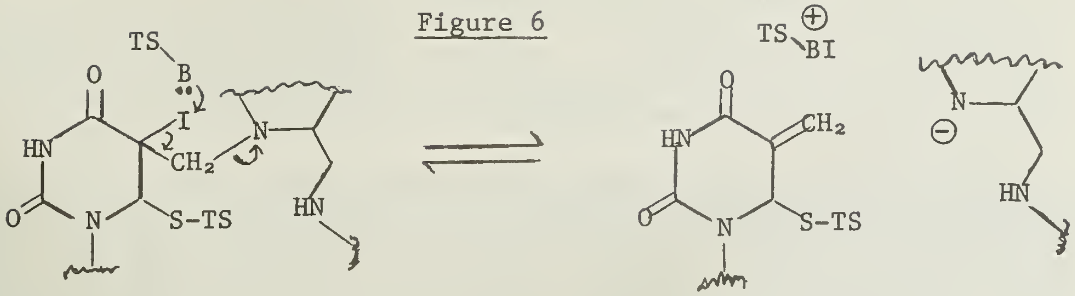
Figure 5



Studies on the position of equilibrium of 1,3-dimethyl-5-nitrouracil and various nucleophiles support this hypothesis.[31]

An interesting case of this type of interaction occurs among the larger halogenated dUMP's. Both 5-bromo- and 5-iodo-2'-deoxyuridine monophosphate actually act as substrates in the TS reaction in marked contrast to the fluoro and chloro analogues.[32] This is difficult to rationalize unless one assumes that the larger, more polarizible halogens can be abstracted by a nucleophile in the active site as illustrated in Fig. 6. In this case dTMP would be produced in the normal way.[32] If the halogenated enzyme can be somehow regenerated then the catalytic cycle can continue. Clearly further study is needed to confirm (or rule out) this hypothesis.

Figure 6

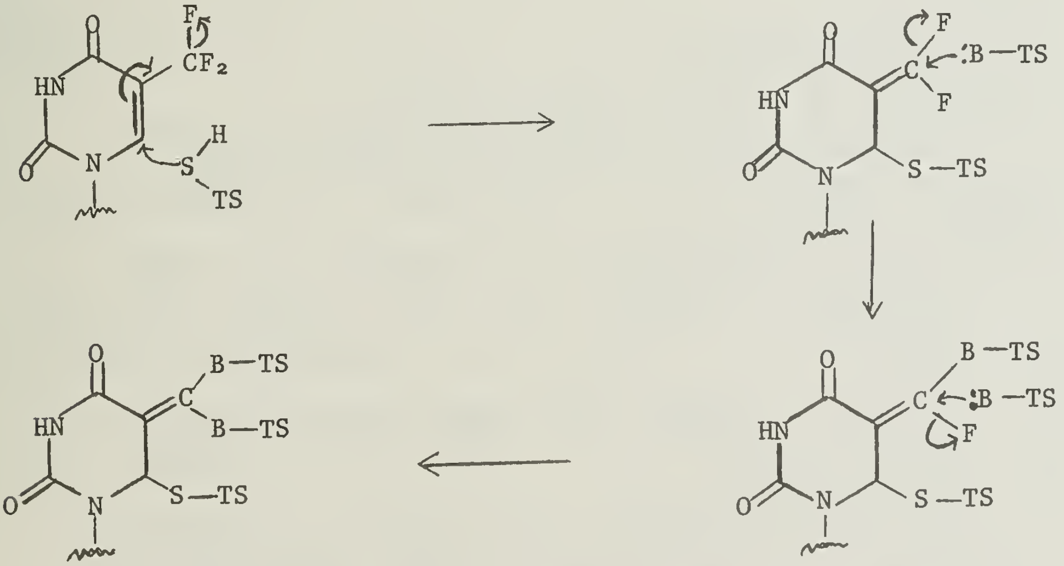


iii) irreversible covalent modification

Inhibitors of this type compete with the natural substrate for the binding site on TS, but once bound are able to form a covalent bond via a reaction off of the normal enzymatic pathway. In this way the enzyme is bound to the inhibitor in an unnatural covalent way preventing binding of natural substrate. With judicious choice of latent functionality on the inhibitor, this modification can be made effectively irreversible.

The earliest attempt to inactivate TS in this way utilized 5-trifluoromethyl-2'-deoxyuridine monophosphate[33] (CF_3-dUMP). This compound competed favorably with dUMP for the TS active site (Ki=0.039uM)[20] and once bound inactivated the enzyme. This inactivated enzyme cannot be regenerated by dialysis[33] (in contrast to F-dUMP). Santi[21,34] suggests that upon nucleophilic addition to C-6, fluoride anion is displaced from the CF_3 group forming the reactive difluoro alkene which can alkylate, irreversibly, some active site nucleophile (Fig. 7). Release of fluoride has been observed upon incubation of CF_3-dUMP with TS.[21]

Figure 7



A clever extension of this principle utilizes vinylogues of (CF_3-dUMP) which maintain the same reactivity pattern as the parent compound but now can extend the range of the reactive function to "find" more distant nucleophiles. The first member of this series (CF_3-$(CH=CH)_n$-dUMP) where n=1 has been prepared and is also an irreversible inactivator of TS.[35]

A distinct type of inactivation may be in effect in the case of 5-formyl-2'-deoxyuridine monophosphate. Although little work has been done to elucidate the mechanism involved here, it has been suggested that after initial competitive binding (Ki=0.017uM),[20] a Schiff base is formed at the active site resulting in the observed inactivation.[36]

Compounds with more remote functionality have also been prepared. 5-α-bromoacetyl-2'-deoxyuridine monophosphate, for example, has been reported to irreversibly inactivate TS after binding (Ki=4uM).[37] Again this is attributed to alkylation of some internal nucleophile. A similar compound, 5-(iodoacetamidomethyl)-2'-deoxyuridine represents a very important advance in this type of inhibition.[38] When this compound is incubated with TS isolated from calf thymus, only competitive inhibition is observed (Ki=27uM). However, when the same experiment is done substituting TS from Ehrlich ascites tumor cells, irreversible modification occurs. This represents the first time that this kind of inhibition selectivity has been seen for any TS inhibitor.

Conclusion. Though many questions remain unanswered in the mechanism and inhibition of TS, much of the work described herein has resulted in important clinical advances in the treatment of various disorders. F-dUMP, for example, has enjoyed wide clinical use in breast cancer, colon cancer, and leukemia patients, both alone and in concert with other agents such as methotrexate. I-dUMP, on the other hand, has proven to be a very effective antiviral compound. These and other tangible successes serve to illustrate the fruitful nature of research in the area of thymidylate synthetase inhibition.

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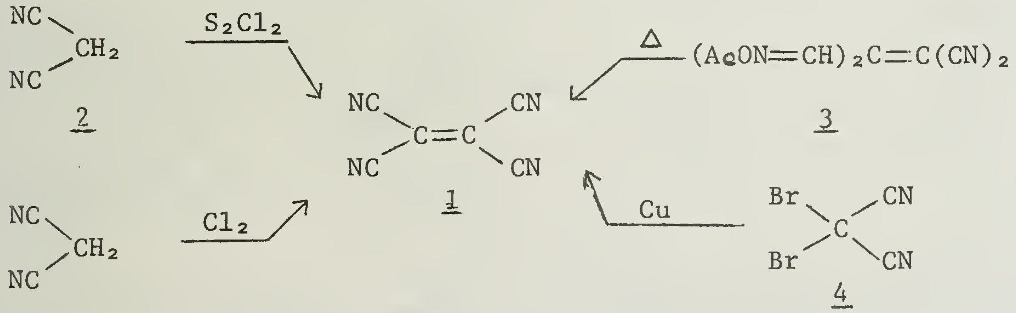
THE CHEMISTRY OF TETRACYANOETHYLENE

Reported by A. Bashir-Hashemi December 1, 1980

Tetracyanoethylene (TCNE) is a versatile compound of exceptional reactivity.[1] For the purposes of this abstract, emphasis has been given to recent developments in the chemistry of TCNE, e.g., heterocyclic formation, cycloaddition and ene reactions.

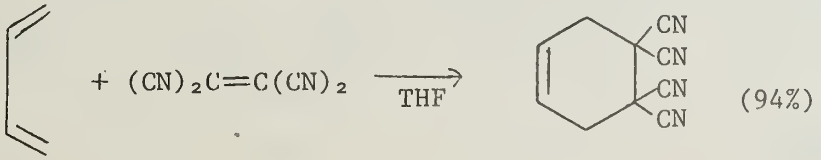
Tetracyanoethylene 1 has been prepared from malononitrile 2 by four different methods.[1] The original preparation consisted of the interaction of malononitrile with sulfur monochloride, in boiling 50/50 chloroform-tetrachloroethylene. A second method involves the vapor phase chlorination-dehydrochlorination of malononitrile at 450°C. The preparation of TCNE has also been accomplished by the condensation of malononitrile with 1,3-bis(acetoxyimino)-2-propanone, followed by pyrolysis of the adduct 3. However, the preferred synthetic preparation of TCNE (62% yield) is the debromination of the KBr complex of dibromomalononitrile 4 with copper powder in boiling benzene. The reaction is believed to involve an intermediate dicyanocarbene, which dimerizes to tetracyanoethylene.[1] TCNE is a colorless crystalline solid and melts at 198-200°C. TCNE slowly evolves hydrogen cyanide when exposed to moist air at room temperature.[2]



Formation of Heterocyclic Compounds. TCNE is a useful starting material for the syntheses of five or six-membered heterocycles, with one or two heteroatoms.[1] Thiophenes, pyrroles, isoxazoles, pyrazoles, pyrimidines and pyridines may all be synthesized from TCNE. For example, addition of hydrogen sulfide to TCNE in the presence of a base gives a cyclized product, 2,5-diamino-3,4-dicyanothiophene 5, which can be rearranged to a mercaptopyrrole 6 under the influence of alkali.

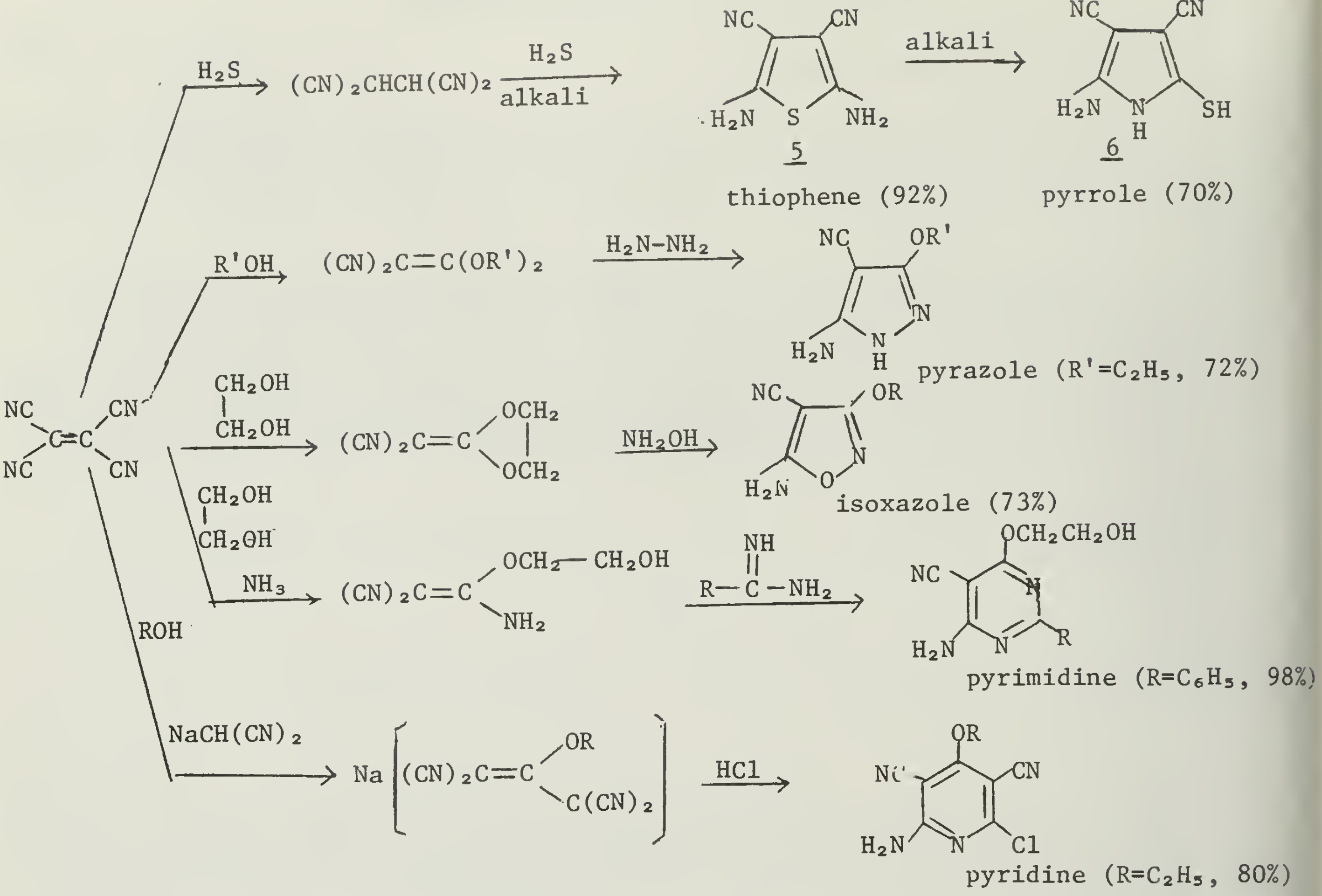
Some of the unique reactions of TCNE are given in Scheme I.[1]

Diels-Alder Cycloaddition Reactions. TCNE is a reactive dienophile and undergoes a $4\pi + 2\pi$ cycloaddition reaction with conjugated dienes such as butadiene and anthracene. Thus when butadiene is added to TCNE in THF at 0°C, the solution first takes on the bright yellow color of the π-complex, and then gives way to the colorless cycloadduct. Tetracyanohexene 13 begins to separate in nearly quantitative yield.[3]

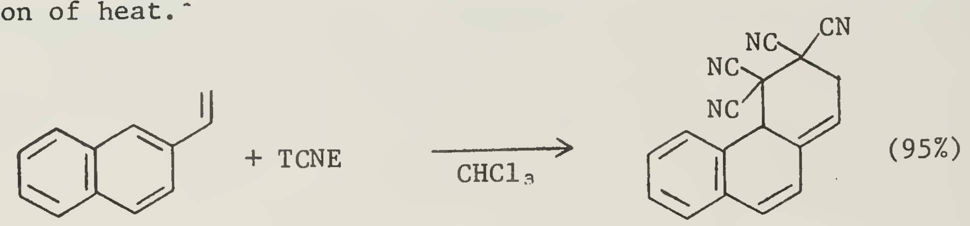


13

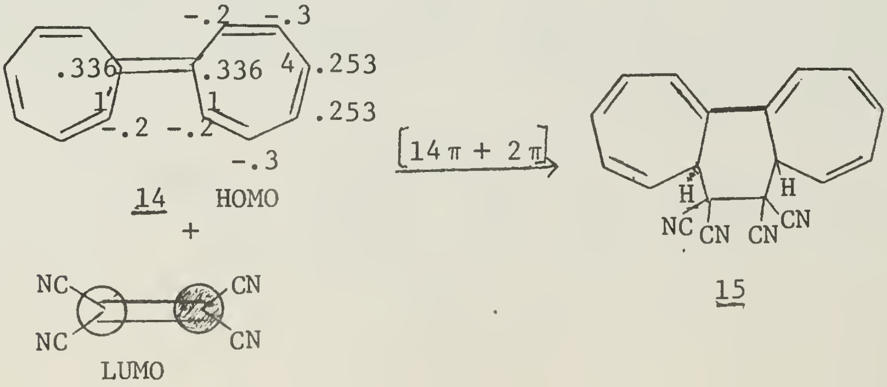
Scheme I


H₂S
(CN)₂CHCH(CN)₂
H₂S
alkali
alkali
5
thiophene (92%)
6
pyrrole (70%)
R'OH
(CN)₂C=C(OR')₂
H₂N-NH₂
pyrazole (R'=C₂H₅, 72%)
CH₂OH
CH₂OH
(CN)₂C=C
OCH₂
OCH₂
NH₂OH
isoxazole (73%)
CH₂OH
CH₂OH
NH₃
OCH₂—CH₂OH
NH₂
R—C—NH₂
NH
pyrimidine (R=C₆H₅, 98%)
ROH
NaCH(CN)₂
Na
HCl
pyridine (R=C₂H₅, 80%)

TCNE will react with dienes such as 2-vinylnaphthalene. This unusual cycloaddition occurs spontaneously and rapidly without added catalyst or application of heat.[1]

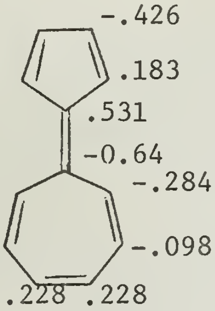

+ TCNE
CHCl₃
(95%)

Geometry Effect on Diels-Alder Reactions. In addition to the frontier orbital factors, geometry plays an important role in the novel $(14\pi_b + 2\pi)$ cycloaddition of TCNE and heptafulvalene 14 to give the adduct 15.[4b] The HOMO coefficients for heptafulvalene are highest at the central bond,[4c] but any

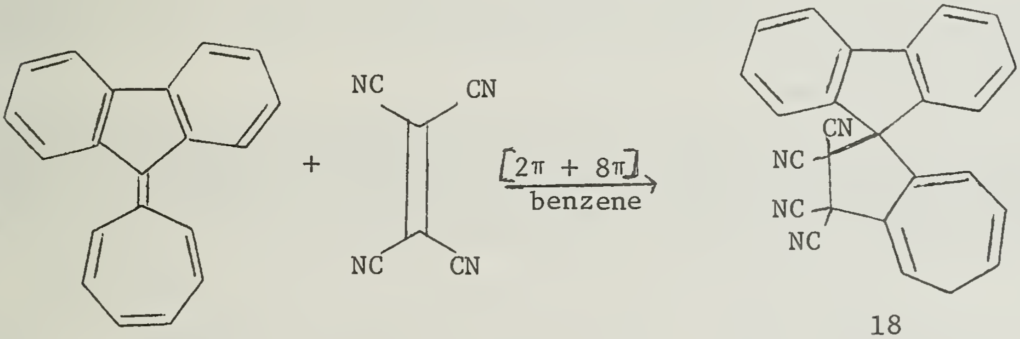

.336
.336
1'
1
4
-.2
-.3
.253
.253
-.2
-.2
-.3
14
HOMO
+
LUMO
[14π + 2π]
15

reaction at this site would have to be, as a result of the orbital symmetry, antrafacial on one of the components, and this is geometrically unreasonable under modest reaction conditions. A Diels-Alder reaction across the 1,4 positions would be another possibility, but this evidently does not occur, probably because the carbon atoms are held too far apart. The only reasonable pathway for cycloaddition which remains is the addition of TCNE to the carbons adjacent to the central double bond (1,1') in 15. By orbital symmetry this reaction must also proceed antrafacially with respect to one of the π-systems, however, the heptafulvalene can easily assume the appropriate geometry.[4]

Sesquifulvalene 16 presents another case where frontier orbital control does not govern regioselectivity. The sesquifulvalene 17 does give the adduct 18 with TCNE,[5] as expected from the coefficients of the HOMO of the unsubstituted system.[4c] However, the sesquifulvalene 19 gives a [12π + 2π] adduct 20 instead,[5] while the sesquifulvalene 21 gives a [4π + 2π] adduct 22.[6]



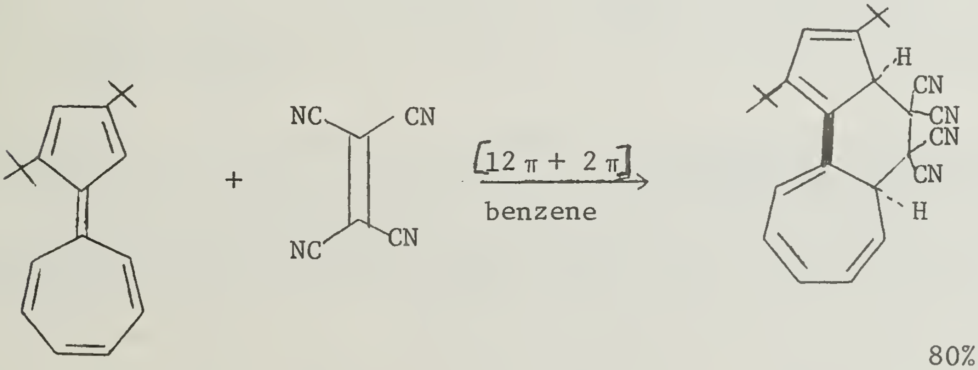
16 HOMO



17

18

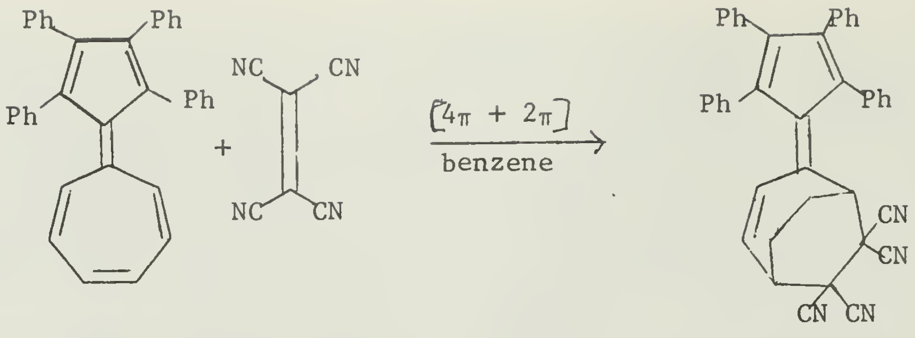
50% yield



80% yield

19

20

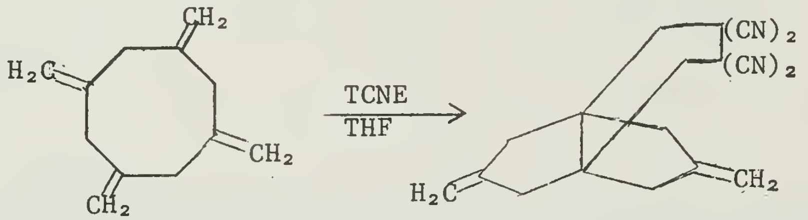


21

22

83% yield

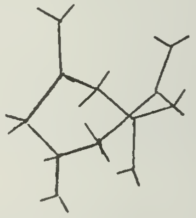
Another interesting cycloaddition is the reaction of TCNE with allene tetramer (1,3,5,7-tetramethylene cyclooctane 23). Here, TCNE undergoes a 1,7-addition to give the tricyclic compound, 24, formed by a ($\pi_{2s} + \pi_{2s} + \pi_{2s}$) trans annular cyclization.[7] Studies of 23 with molecular models indicated that



23

24

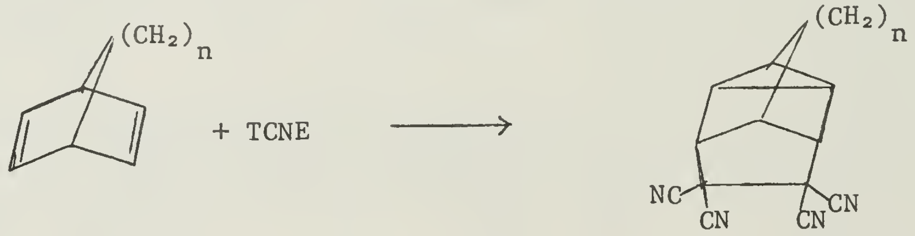
85% yield



23a

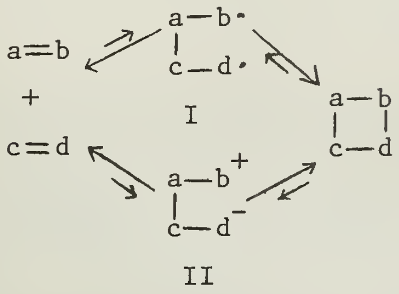
the conformation, 23-a, places opposite pairs of double bonds parallel to one another at a distance of about 2.7 Å. It appeared that at this distance there is appreciable π-orbital interaction of the double bonds in each pair and thus the compound might exhibit enhanced reactivity of a kind normally associated with conjugated systems.

Reaction of TCNE with bicyclo [2,2,n] alkadienes has been investigated.[8,9] TCNE reacts with bicyclo [2,2,n] alkadienes (n=1,2) in CH_2Cl_2 in a $[\pi_{2s} + \pi_{2s} + \pi_{2s}]$ HOMO-Diels-Alder fashion. For (n=3,4) no addition has been observed.



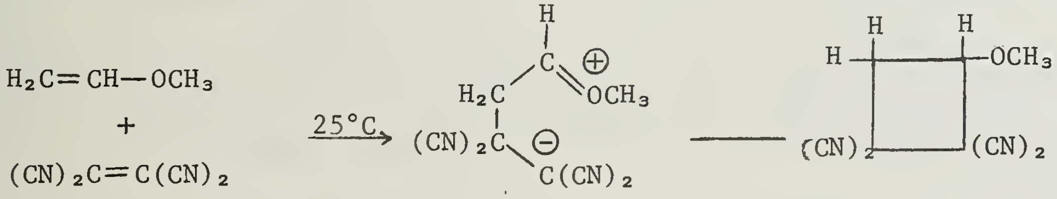
(2π + 2π) Cycloaddition. Thermal (2 + 2) cycloaddition leading to four-membered rings are less frequently encountered than 4π + 2π cycloaddition reactions. The suprafacial combination of two π-bonded systems, $\pi_{2s} + \pi_{2s}$, is not expected to be energetically favorable due to orbital symmetry.[10] These reactions are usually restricted to allenes, ketenes, polyhaloethylenes, conjugated dienes, and strained hydrocarbons.[11] It is generally assumed that the concerted (2 + 2) cycloaddition is by-passed and the two new σ bonds are formed in a stepwise fashion. The reverse type of process, the rupture of a four-membered ring to form two alkene molecules, should also occur in a nonconcerted fashion.[12,13]

Two different pathways have been proposed for thermal (2 + 2) cycloaddition reactions, a singlet biradical (I) or a zwitterionic tetramethylene derivative (II).[13]



Bartlett's masterful investigation of cyclobutane formation from 1,1-dichloro-2,2-difluoro ethylene and from the cis, trans isomeric hexa-2,4-dienes demonstrated the biradical course to be operate.[12]

Cyclobutane formation by reaction of TCNE with enole ethers proceeds, according to R. Huisgen's investigations, via a zwitterion type intermediate, 24.[13]



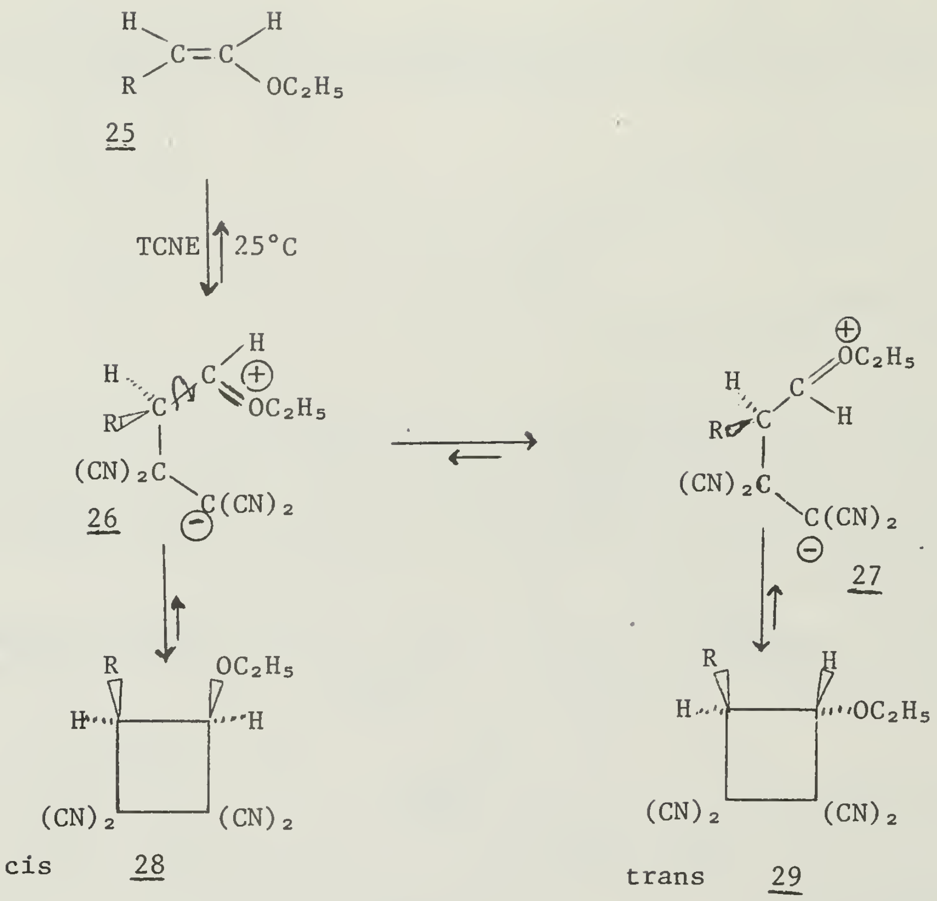
24

90% yield

The fact that simple alkenes and the double bond of acrylic esters are inert to TCNE does not support a biradical intermediate of Type (I), but lends support to the zwitterion (II). Structure 24 illustrates the efficient charge stabilization of the presumed intermediate from methyl vinyl ether and TCNE.

The facile reaction of TCNE with ethyl cis-1-alkenyl ether, 25 produced quantitatively two cyclobutane derivatives.[14] The configuration of the alkenyl ether is retained in the major product, 28, while the NMR chemical shifts of the minor product leave no doubt that it has the trans structure, 29. In terms of the zwitterion mechanism, rotation about the marked bond of 26 begins to compete with cyclization.

The amount of stereochemical integrity lost increases with solvent polarity.[16] Thus, starting from R=C_2H_5, one obtains 2% of the trans product in benzene, 7% in dichloromethane, 10% in ethyl acetate, and 18% in acetonitrile. A longer lifetime for intermediates 26 and 27 in a more polar solvent due to better solvation and diminished coulomb attraction of the charge centers, appears to be responsible for this outcome.

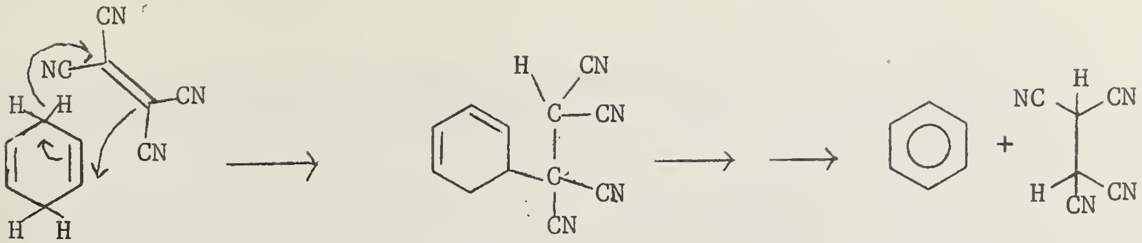


The rate of TCNE cycloadditions is immensely dependent on solvent polarity;[15] K (acetonitrile)/K (cyclohexane) amounts to 63,000 for 4-methoxystyrene, 29,000 for anethole and 2600 for butyl vinyl ether. Such large dependencies appear to be unique among cycloadditions, and this fits one's expectation for a zwitterion intermediate formation.

Ene Reactions. Although the Alder-ene reaction is quite common with simple alkenes,[16] it occurs relatively infrequently with conjugated dienes because most good enophiles are also effective Diels-Alder dienophiles.

Ene reactions are seen with constrained dienes which cannot achieve the syn arrangement required for the Diels-Alder reaction.[17, 18, 19] Although the ene reaction also appears to be subject to steric influency, probably due to the preferred orbital geometry for the concerted hydrogen transfer.[20] While TCNE reacts with cyclopentadiene in a $(4\pi + 2\pi)$ cycloaddition manner, it reacts with 1,3-cyclohexadienes 31[23] and 1,4-cyclohexadiene[22] through the ene reaction.

The aromatization of cyclohexadienes with TCNE is a very mild reaction that has seen occasional synthetic use.[19,21] Equimolar amounts of 1,4-cyclohexadiene and TCNE in boiling dioxane give benzene in 98% yield.[21] B. M. Jacobson has investigated the aromatization of 1,4-cyclohexadiene with TCNE.[22] The aromatization is actually initiated via an ene reaction to give 5-(1,1,2,2-tetracyanoethyl)-1,3-cyclohexadiene, 30. The elimination of tetracyanoethane from 30 produces the aromatized product.

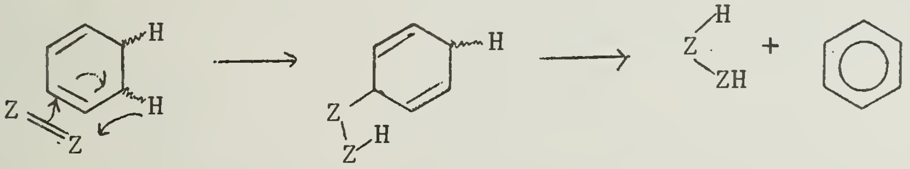


30

In both THF and acetonitrile-d_3 the disappearance of 1,4-cyclohexadiene is a second-order reaction, first order in 1,4-cyclohexadiene and first order in TCNE. The rate constants at 35°C are 5.3×10^{-3} $LM^{-1}min^{-1}$ and 6.4×10^{-2} $LM^{-1}min^{-1}$, respectively. The conversion of the intermediate 30 into benzene follows first-order kinetics with rate constants $3.87 \times 10^{-4} min^{-1}$ in THF and $1.62 \times 10^{-3} min^{-1}$ in acetonitrile-d_3.

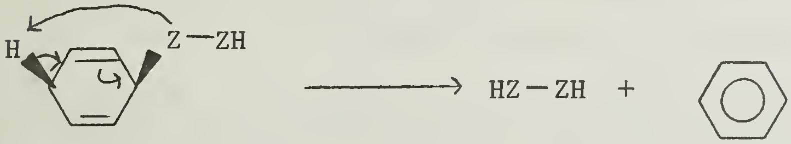
As to the further mechanistic details of the formation and decomposition of 30, it should be noted that there is a modest color change upon mixing the TCNE and 1,4-cyclohexadiene presumably from a charge-transfer complex being formed. The tenfold increase in the rate constant for formation of 30 on going from THF to CD_3CN might be considered support for a rather more polar transition state than usual in the ene reaction. The merely fourfold increase in the decomposition rate of 30 would seem small if the reaction proceeds through dissociation to cyclohexadienyl cation, but a preliminary run in a 65:35 acetone-water mixture showed a further large rate increase.[22]

In the case of 1,3-cyclohexadienes, 31, three mechanisms have been formulated for the elimination step,[23] an isoretero-ene reaction($\sigma^2 + \pi^2 + \sigma^2$) (Eq. 2), a simple homolytic one (Eq. 3), and a heterolytic reaction (Eq. 4).

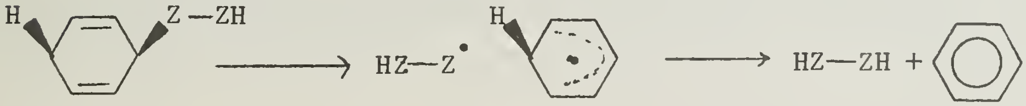


31

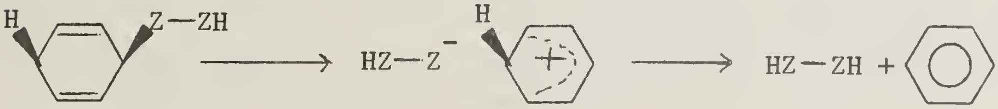
$Z{=}C(CN)_2$ (1)



(2)

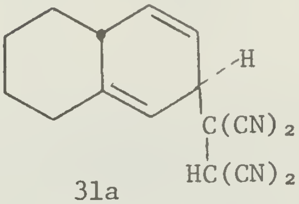


(3)

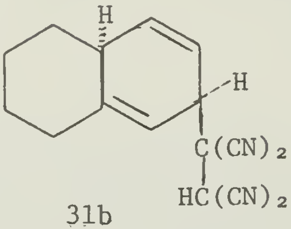


(4)

As it was tempting to suspect concerted decomposition as in Eq. 2, compound 31b was prepared for comparison.[23] In the latter, the trans arrangement of the tetracyanoethyl group and the departing hydrogen preclude a concerted intramolecular elimination. However 31a and 31b were found to decompose at comparable rates (see Table 1). Further, the rate constant was strongly dependent on solvent, with marked enhancement in both protic and aprotic polar solvents.



31a



31b

Table 1. Variation in Decomposition Rates of 31a and 31b with Solvent Polarity at 35°C

adduct	solvent	rate constant x $10^6 s^{-1}$
31a	ether	1.5
31a	acetone	41
31a	ethanol	170
31a	acetone/D_2O 75:25 v/v	270
31b	acetone	36
31b	dimethylformamide	210
31b	acetone/D_2O 75:25	460

These results suggest the heterolytic path to be in effect.

Uses of TCNE. The uses of TCNE include inhibition of polymerization, the aromatization of certain nonconjugated cycloalkadienes and increasing the photosensitivity of some organic dyestuffs. It has also been used in the determination of aliphatic, alicyclic, aromatic 1,3-dienes, phenols, and aryl ethers, analogous to the broad utility of metal-EDTA chelates in inorganic analysis. TCNE, like EDTA, is a fairly general complexing agent and reacts rapidly under mild conditions.

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REMOTE FUNCTIONALIZATION REACTIONS

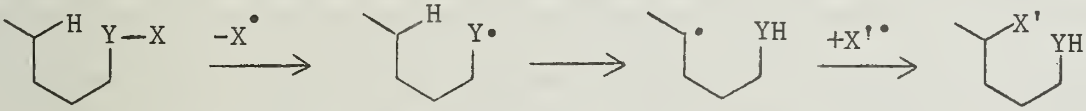
Reported by Venkatesalu Bakthavachalam December 4, 1980

Enzymic reactions bring about highly selective transformations at extraordinarily high rates. The most intriguing feature of enzyme catalyzed reactions is their remarkable regioselectivity, especially those involving transformations at centres which are not activated in the usual chemical sense. A typical example for this kind of transformation is the selective dehydrogenation of stearic acid to oleic acid (Eq. 1). Selectivity of this nature is

$$CH_3(CH_2)_{16}COOH \xrightarrow[\text{phlei}]{\text{Mycobacterium}} CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH \qquad (1)$$

believed to be the result of geometrical restrictions imposed in the enzyme-substrate complex which fits only certain substrates and where only certain points in the substrate molecule can be attacked. In contrast, chemical reactions almost always occur at sites which are dictated by an already present functional group. As an attempt to mimic the selectivity of enzymic reactions, there have been interesting investigations of functionalization at non-activated centres or reactions at positions remote from the functional group.[1]

A number of intramolecular free radical reactions have been observed which involve the formation of a reactive hetero atom radical in a molecule, which then abstracts a hydrogen atom attached to a δ-carbon atom, thus initiating functionalization at a non-activated site (Eq. 2).[2] The Barton reaction,[3] which involves the photolysis of alkyl nitrites, belongs to this category. The mechanism of this reaction has been investigated[4] and the procedure has been employed in many useful transformations in steroids,[5] terpenes,[6] and other natural products.[7] In a related reaction Cekovic reported the formation of remote olefinic bonds by a metal catalyzed decomposition of hydroperoxides and alkyl nitrites.[8]

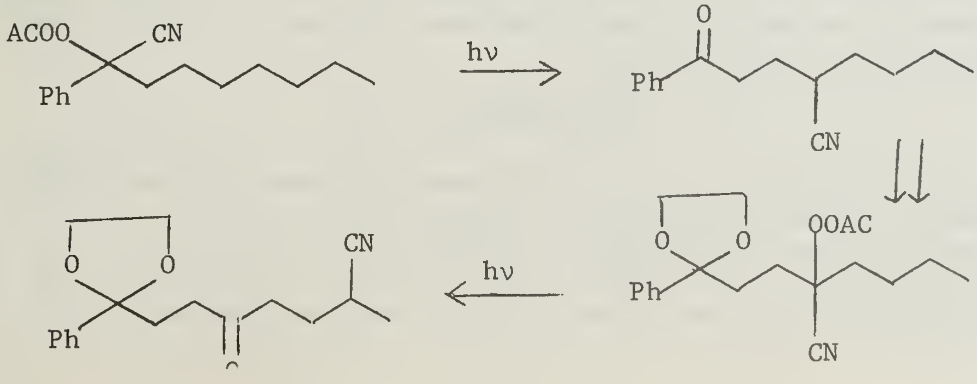


(2)

Y=O, N; X=halogen, NO, OH, $Pb(OCOCH_3)_3$

A new photochemical reaction reported by Watts and coworkers has the advantage of reiterative functionalization; a parent functional group migrates down the backbone of the substrate regioselectively and leaves behind a daughter functional group (Scheme I).[9] This reaction has been applied to functionalize

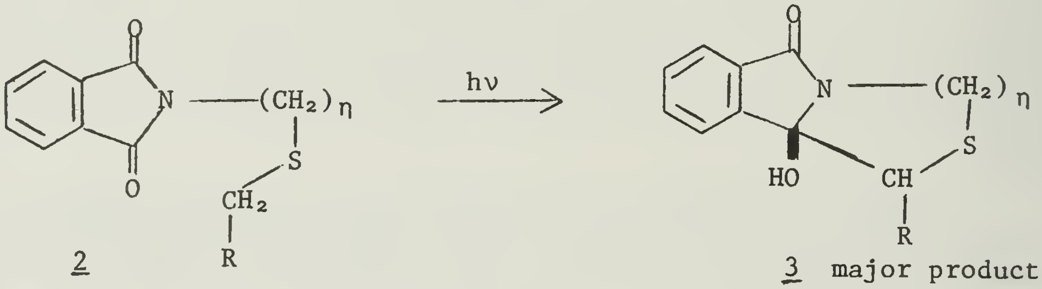
Scheme I



non-activated methyl groups in steroids.[10]

Money and coworkers investigated the remote oxidation of terpenes,[11] fatty acid esters,[12] and macrocyclic acetates and macrolides[13] with chromium trioxide. Their approach is based on the notion that certain molecules are intrinsically susceptible to oxidation at centres which are generally considered to be unreactive. Lactones and cyclic ketones were formed by the remote oxidation of carboxylic acids by peroxodisulfuryldifluoride[14] and by direct anodic oxidation.[15] Ferrous ion has been found to induce stereospecific hydroxylation in cyclohexanol[16] and remote oxidation in the decomposition of a rigid epidioxide.[17]

Certain phthalimides (2) with terminal sulfide functions bearing N-alkyl side chains undergo regioselective photocyclization to give azathiacyclols (3).[18] This reaction has been utilized in a facile synthesis of medium to large size ring systems including analogs of cyclic peptides, lactones and crown ethers.[19]



Breslow and coworkers have devised a series of remote functionalization reactions.[20] The principle behind this study is the directed functionalization of the substrate at a remote site, the selectivity being determined by the geometry of an associated reagent, catalyst, or template. Photolysis of attached or complexed benzophenone groups has been employed in the remote oxidation of long-chain alcohols[21] and steroids.[22] Selective halogenation of steroids has been achieved by using attached aryl iodide templates.[23] Few related remote functionalization reactions were reported by other workers.[24] Template directed remote epoxidation of olefins[25] and the selective epoxidation of arachidonic acid has also been observed.[26]

Remote functionalization reactions serve as conformational probes for flexible alkyl chains,[27] micelles,[28] and for model membrane systems.[29] Winnik has developed a computer simulation program for predicting the sites of attack in the remote oxidation reactions of fatty acid esters and long chain alcohols.[30]

As we have seen, remote functionalization reactions add a new dimension to organic synthesis. Even though the methods listed so far may not be generally applicable, continued interest in this area will certainly enhance our ability to perform chemical transformations which mimic both the style and selective results of biochemistry.

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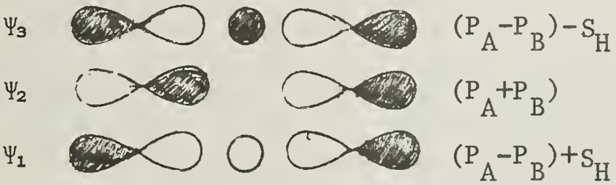
HYPERVALENT HYDROGEN

Reported by Charles Perkins December 11, 1980

The significance of the chemistry of hydrogen is obvious. What is less obvious is that much of this chemistry can be viewed as a consequence of a hydrogen centered, three center, four electron (3c,4e) hypervalent bond. Many aspects of the chemistry of sulfuranes, phosphoranes, numerous other types of hypervalent compounds, as well as bimolecular substitution reactions on carbon, are effectively explained in terms of 3c,4e bonding. Various features of hydrogen chemistry are also made more tractable when the central role of this ubiquitous bonding arrangement is recognized.

An early recognition of the applicability of the 3c,4e bonding description to hydrogen chemistry is exemplified by Pimentel's[1] M. O. description of the bifluoride ion $(HF_2)^-$. In this description the four bonding electrons fill the two lowest energy orbitals (Ψ_1 and Ψ_2) formed by the combination of two 2p orbitals (one on each fluorine) and the 1s orbital of hydrogen (Figure 1).

Figure 1. An approximate M.O. scheme for hypervalent hydrogen



When interpreting hydrogen chemistry in terms of a hypervalent bonding structure, there are a number of interesting features that it would be well to remember.

1) Since only one orbital is bonding, Ψ_1, the overall bonding order of each single bond will be less than a normal covalent bond, while the bonding distances are expected to be longer; 2) A continuum of degrees of hydrogen bonding can be described simply by varying the coefficients in the manner shown in Figure 2. As b coefficients decrease from unity to zero the atom "B" is moved away from the symmetry position; 3) An accompanying attribute of electronegativity is the degree to which an atom or group of atoms may accommodate electron density with a minimum increase in energy. Since

Figure 2. Non-normatized description of various kinds of hydrogen bonds

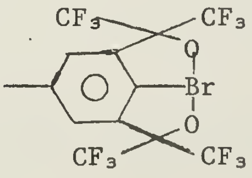
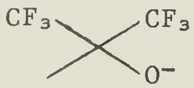
Strong centered H bond	Unsymmetric H bond of varying strength	No H bond
$(P_A - P_B) - a_3S$	$(P_A - b_3P_B) - a_3S$	$P_A - a_3S$
$P_A + P_B$	$b_2P_A + P_B$	P_B
$(P_A - P_B) + a_1S$	$P_A - b_1P_B + a_1S$	$P_A + a_1S$
A—H—B	A—H——B	AH :B

the orbitals comprising Ψ_2 concentrate virtually all of the electron density on the outer two atoms, the more electronegative are A and B, the more stable will be this bonding structure; 4) Since the 1s orbital of the central hydrogen is employed, rather than a p orbital (which is what is utilized in the linear hypervalent bonding with other central atoms) the hypervalent hydrogen bond may deviate from linearity to a large degree without a concommitant loss of stability. A large departure from linearity, which in other systems would significantly reduce overlap with the central p orbital, is not seen in the otherwise equivalent hypervalent bonds of the trihalides; 5) A similar overall bonding order would be expected if only three electrons occupied Ψ_1 and Ψ_2. A three electron system centered on sulfur has been postulated[2] to exist for sulfuranyl radicals. It is a tantalizing model to apply to hydrogen atom abstraction; 6) Placing two electrons in this system describes the now familiar hypovalent bonding in boranes.

Bifluoride. Stable, isolable hypervalent hydrogen species are known under the guise of "strong" hydrogen bonds. Given the stabilizing effect of electronegativity on the outer atoms in the hypervalent bond, it is not surprising that bifluoride, $(HF_2)-$, is among the most stable hypervalent hydrogens. The unusual strength of this hydrogen bond was first implied by the results of an x-ray study as early as 1923.[3] This evidence for the strength of this hypervalent bond, the short R(F...F) distance of 225 pm for potassium difluoride, has since been further confirmed by data from the various studies used to detect strong hydrogen bonds.[4] Outright measurement of bond strengths have provided a variety of values ranging from 152 kj/mole (36.3 kcal/mole) to 243 kj/mole (58.1 kcal/mole). Theoretical calculations have varied from 167 kj/mole (39.9 kcal/mole) to 234 kj/mole (55.9 kcal/mole).[4] These values fall in the range of covalent bond strength.

Ligands. Comparisons between hypervalent systems can be fruitful. One interesting parallel is between apicophilicity and hypervalent hydrogen bond strengthening character. Although all of the factors that determine the apicophilicity of ligands in ψ-TBP structures are not present in strong hydrogen bonded molecules, there is a striking resemblance between the kinds of chemical species that form strong hydrogen bonds and those that preferentially occupy apical positions. Of the five brominanes extant (Table 1) the first four of them have apical ligands which are among those species that form the strongest of hydrogen bonds (Table 2). Phosphorane apicophilicity[6,7a]

Table 1

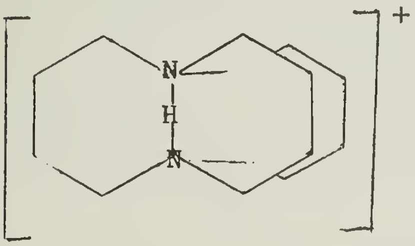
Brominane	Apical ligand	ref.
BrF_3	F^-	5a
$Br(ONO_2)_3$	ONO_2^-	5b
$Br(FSO_3)_3$	$(FSO_3)^-$	5c
		5d
$B(FSeO_3)_3$	$(FSeO_3)^-$	5e

and sulfurane apicophilicity[7b,8] parallel hypervalent hydrogen bond strengthening capacity. A notable exception to this trend is the strong apicophilicity of hydrogen in phosphoranes. A significant factor in hydrogen's propensity to occupy the apical position in phosphoranes is its lack of steric bulk. The fact that sulfur is more electronegative than hydrogen renders unfavorable an apical occupancy by hydrogen in sulfuranes. Whether a strong hydrogen bonded species containing two hydrogens can be synthesized remains to be seen.[14] The well-known candidates for apical occupancy (halogens, oxygens and nitrogen ligands) are also those that form strong hydrogen bonds. Representatives are shown in Table 2.

Table 2

Strong H Bond	R(X...X)	Detection Method	∢ Van der Wall's R	Ref.
$\mathrm{Cs(CF_3\overset{O}{\overset{\|}{C}}O)_2H}$	238 pm	x-ray	62	9a
$\mathrm{K(CF_3\overset{O}{\overset{\|}{C}}{-}O)_2H}$	243.7 pm	x-ray neutron	57	9b
$\mathrm{K(CH_3\overset{O}{\overset{\|}{C}}{-}O)_2H}$	247.6 pm	x-ray	53	9c
$\mathrm{K(H{-}\overset{O}{\overset{\|}{C}}{-}O)_2H}$	244.4 pm	x-ray	56	9d
$\mathrm{K(F{-}H{-}F)_2H}$	227.7 pm	neutron x-ray	63	9e
$\mathrm{Cs(Cl{-}H{-}Cl)_2\ 1/3\ H_3O^+}$	314 pm		36	9f
$\mathrm{Cs(Br{-}H{-}Br)_2\ 1/2\ H_3O^+}$	335 pm			9g
$\mathrm{Cs(NO_3{-}H{-}NO_3)}$	246.8 pm	x-ray neutron	55	9h
$\mathrm{K(ØCH_2\overset{O}{\overset{\|}{C}}{-}O{-})H}$	244 pm	x-ray	56	9i
$\mathrm{Br^-}$ $\mathrm{{}^{H}_{H}{>}O{-}H{-}O{<}^{H}_{H}}$	240 pm	neutron	60	9j
$\mathrm{K(Cl_2H\overset{O}{\overset{\|}{C}}{-}O{-})H}$	237 pm		63	9a
$\mathrm{K(pClC_6H_4O_2)HPO_2H_3C_8(CN)_6}$	258.2 pm	x-ray	41	9k
$\mathrm{NaH(SO_4)_2}$	243.4 pm		56	9l

Cyclic structures. Inclusion of the hypervalent atom in a five-membered ring linking an apical and an equitorial position has been shown to be a stabilizing influence in hypervalent compounds.[7a,b] This effect may be subsummed under the general category of ring strain effects. In the context of ring stabilization, however, the hydrogen case differs from other cyclic systems because in hydrogen cyclic systems the ring must include two apical positions. The flexibility of the hydrogen hypervalent bond and the shorter distances involved allow this structural idiosyncrasy to exist. There are a number of very stable molecules with hydrogen included in a cyclic system. Besides the three representatives below, 1, 2, 3,[11] numerous oximato complexes, 4, have very short R(O...O).[4] It is worth noting that the neutral zwitterion



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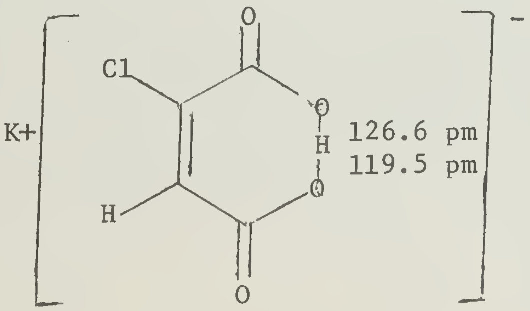

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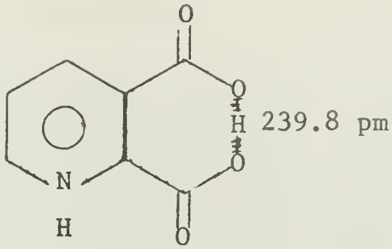

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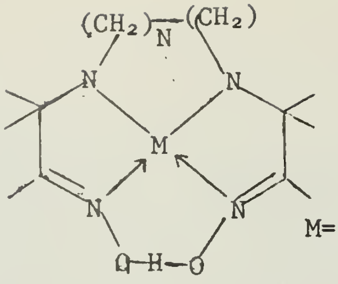

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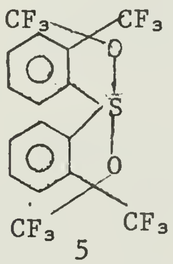
3 has the shortest R(O-O). One of the best suited ligands for stabilizing sulfuranes, brominanes, iodonanes, siliconates, phosphorinanes, and more highly oxidized analogues of some of these compounds, is the hexafluoronated cyclic alkoxy ligand shown in 5, 6, and 7.[12] The low pka of perfluoro pinacol,[13] 5.95 (lowest known for saturated alcohols) is attributable to formation of the stable five membered ring, 8, that bears an obvious resemblance to the compounds containing two "magic"[5d, 12a] ligands. To put this low pka in perspective, it may be compared to the pka of perfluoro-t-butyl alcohol (9.52).



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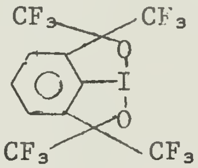

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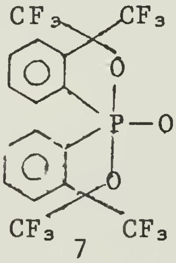

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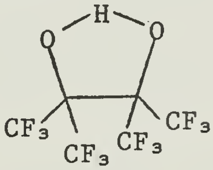

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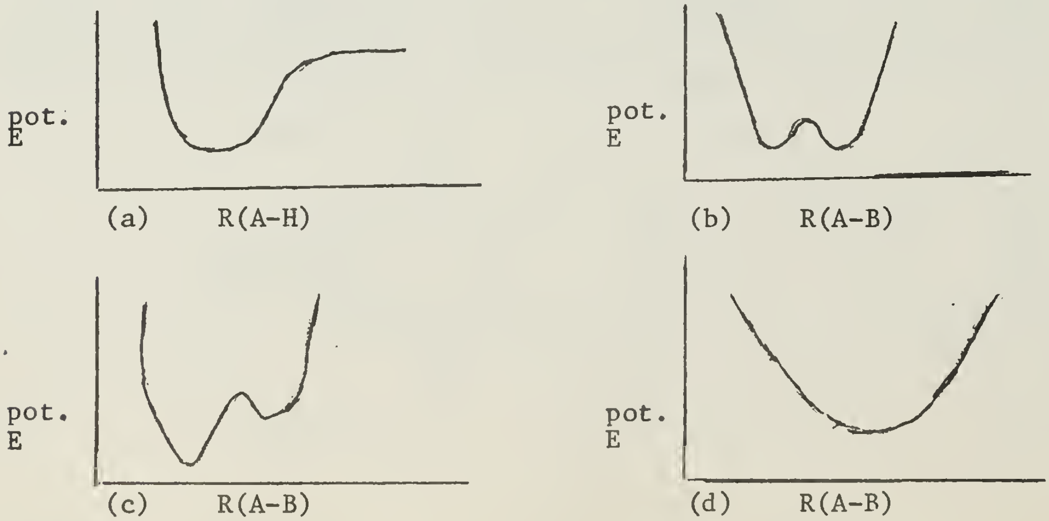
Polarization. Structures of compounds containing unsymmetrical, presumably polarized hypervalent bonds have been determined by x-ray crystallography.[14a] A study[16b] of carbonyl stretching frequencies in variously substituted sulfuranes further attests to the polarized nature of some hypervalent bonds. There are numerous examples of polarized hypervalent hydrogen bonds,[4] but there is a unique feature about the polarizability of hydrogen bonds. Protons are thought to exist in four different types of potential wells.[15]

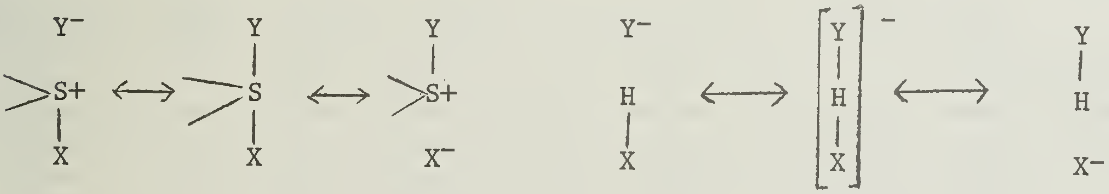
Figure 3. Potential wells for hydrogen containing bonds



When the proton is in certain kinds of 3a, b, or c type potential energy wells, however, it may (unlike other atoms) easily oscillate over a "large" distance. For proton environments that can be characterized by 3b or 3c, the motion, energy levels, transition probabilities and lingering times in each well have been investigated.[16] In this molecular environment the possibility of displacement of a proton causes a polarizability 1-2 orders of magnitude greater than the polarizability due to electronic displacements alone. An important contribution to the unusual mobility of the proton in the hydrogen bond is its tunneling through the energy barrier in the double minimum type of potential.

Another aspect of the polarization of hypervalent bonds is the relative length of each bond in the two bond system. In a hydrogen bond complex the substituent that is the most basic is the one expected to be closest to the hydrogen. The longer bond is the bond that, when broken, results in the smaller loss of energy. This is simply a consequence of the meaning of "stronger" and "weaker" base. The phenomenon of hypervalent bonds being skewed in such a way that the longer of the two bonds is the most energetically favorable to break, has been documented in sulfurane chemistry.[14a] It may be that both phenomena are a consequence of the ligands ability to accommodate a negative charge. This electron distribution can be translated into a hypervalent M.O. description by mixing in a larger coefficient of the P_B orbital into Ψ_2, the non-bonding orbital. This is analogous to a resonance theory description that includes a larger contribution of the appropriate unbonded form (Figure 4).

Figure 4. Resonance description of polarized hypervalent sulfur and hydrogen bonds



Unsymmetrically substituted hypervalent bonds sometimes appear to be stronger than either of the symmetric analogs. Ab initio calculations[17] of the fluoride-formic acid system, diformate, and difluoride, indicate that the fluoride-formic acid complex is the most stable of the three.

More evidence for the added strength of the asymmetric bond is provided by dissociation studies of Jasinski.[18] For a series of substituted carboxylic acids with a given reference anion (e.g., acetate or nitrobenzoate) the value of the K_{AHB} $(=[AHB]^-/[AH][B^-])$ increases with acid strength. Noteworthy in this context is that the trifluoro, dichloro, and other substituted acetic acid-acetate combinations have a greater K_{AHB} than the acetic acid-acetate K_{AHA}. This is another example of a correct prediction based on the hypervalent model. It is not what one would expect from electrostatic considerations alone. There also appear to be some sulfur centered asymmetric hypervalent bonds stronger than their symmetric siblings.[19]

Proton Transfer. During the course of proton transfers, intermediates and/or transition states that include hypervalent hydrogen may occur. Considering the potential wells 3b and 3c may shed some light on the discreet steps of this process. As the abstracting moiety approaches, well 3b (with the depth of the minimas possibly reversed) will describe an intermediate hydrogen bonded complex. The proton's energy will exceed the barrier (or the proton may tunnel through it) forming a proton-transfer complex. The complex may dissociate to leave products. Figure 5 illustrates a possible hypervalent M.O. description of this process. By carefully adjusting the pka of the donors and acceptors, evidence of the intermediates is observed in IR spectra.[20] The results of such a study are given in Table 3. The alcohols are arranged in the order of increasing acidities. The trend in the ν(O-H...N) column indicates increasing hydrogen bonding as do the N-H shifts. Two new bonds appear in the series at p-cresol, which are attributable to the proton transfer complex. For the next three alcohols in this series a tautomeric equilibrium appears between the H-bonded and proton transfer complexes. For the rest, of lower pka (≤8.28) the ν(O-H...N) band doesn't exist. The equilibrium is shifted almost entirely to the proton-transfer complex. Observe the transition from one type of potential energy function to another as the pka was varied. At high pka there was a type 3c function that was replaced by another type 3c function with the second minimum lower than the first. Both complexes may be described by the hypervalent M.O. description using the appropriate coefficients in a manner suggested by Figure 4.

Figure 5. Filled M.O.s of species involved in proton transfer

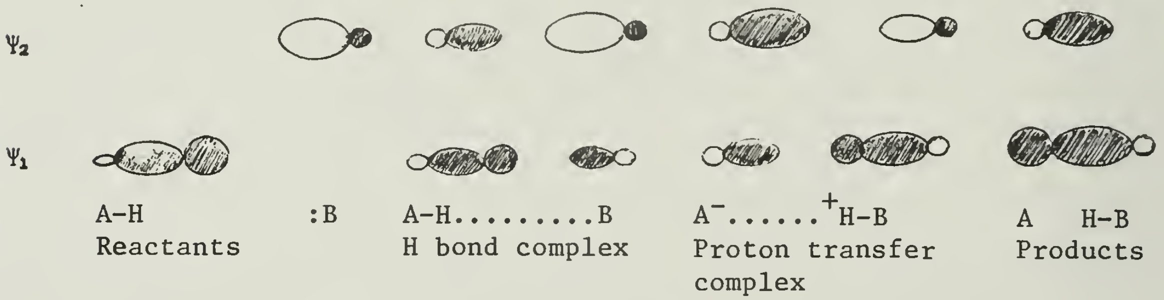


Table 3. Effect of hydrogen bonding on the NH_2 vibrations of n-propyl amine

Donor	Solvent	$\nu(O\text{-}H...N)^a$ cm^{-1}	$\nu(N^+\text{-}H...O)^b$ cm^{-1}	pka	Asym. free $\nu(NH_2)$ cm^{-1}	Asym. Assoc. $\nu(NH_2)$	Asym. $\Delta\nu(NH_2)$ cm^{-1}	Sym. free cm^{-1}	Sym. Assoc. $\nu(NH_2)$ cm^{-1}
2,6-dinitrophenol	benzene	—	2760,2500	3.76	3390	3360	30	3324	3299
p-nitrophenol	benzene	—	2760,2500	7.15	3390	3360	30	3324	3300
m-nitrophenol	benzene	—	2760,2500	8.28	3390	3362	28	3324	3300
p-chlorophenol	CCl_4	3040	2750,2690	9.38	3390	3374	16	3324	3309
phenol	CCl_4	3050	2740,2690	9.95	3390	3375	15	3324	-c
p-cresol	CCl_4	3060	2740,2690	10.19	3390	3378	12	3324	3310
methanol	CCl_4	3282	——	16.60	3390	3382	8	3324	-c
t-butanol	CC14	3322	——	17.62	3390	-c	—	3324	-c

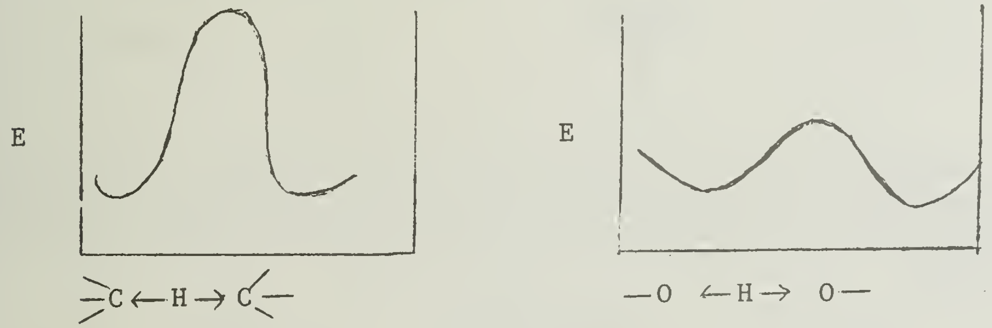
a) Shift in O-H bond due to H-bond
b) The NH_3+ stretching vibration
c) Obscured by the broad (O-H.... N) bond

If the two minima in these potential energy functions are separated by a large barrier the proton transfer rate is expected to be slow. The height of this barrier will reflect the stability of the hypervalent transition state.[21] The maximum in potential energy becomes greater (shown in Figure 6) as those features that stabilize hypervalent hydrogen are reduced. The height of the maximum in a proton transfer between two carbons would be expected to reflect the lesser electronegativity of carbon vs. nitrogen or oxygen. Consequently the rate of transfer between two carbons is substantially slower. A characteristic rate for each is given in Table 4.

Table 4. Proton Transfer Rates

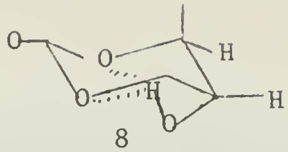
acid	base	solvent	K_F	K_r	ref.
CH_3OH	CH_3O^-	Methanol	1.8×10^{10}	1.8×10^{10}	22a
$(PhCH_2)_2CH_3NH$	$(PhCH_2)_2CH_3N$	DMSO	6×10^8	6×10^8	22b
CH_3SOCH_3	$CHSCOCH_2^-$	DMSO	10	10	22c

Figure 6. Potential energy function for proton transfer between carbon and oxygen



One can imagine hydrogen atom transfer going through a similar process involving 3c, 3e hypervalent hydrogen bond. Such a bond would be expected to have a bond order the same as the 3c, 4e bond. One would therefore predict that a one electron oxidation of bichloride $[Cl\text{-}H\text{-}Cl]^-$ and bibromide $[Br\text{-}H\text{-}Br]^-$ would have a small effect on the bond order. Force constants for both the anions and the neutral molecules have been measured and are quite similar.[23] $[HCl_2]^-$ and HCl_2 have (16 and 14 mdyne/pm). $[HBr_2]$ and HBr_2 have (13 and 14 mdyne/pm). These results would clearly imply Pimentel's description and are not, in any obvious way, predictable from considerations based on either an electrostatic or a charge transfer model.

Bifurcated hydrogen bonds. When hydrogen is bonded to more than two atoms it is said to be in a bifurcated hydrogen bond. A number of crystals (glycine, Tultons salts, 1,3,5-triamino-2,4,6-trinitrobenzene, to name a few) contain bifurcated hydrogen bonding.[24] Few of these unusual structures have been observed in solution. An interesting rarity is the dioxane alcohol 8.[25] The coupling constant $^3J_{HCOH}$ for a dilute solution of 8 is compared to two groups of similar systems in which the dihedral HOCH angles are constrained to be either 180° or 150°. When the angle is 180° the coupling constants are in the range of 12.0 Hz to 12.5 Hz. When the angle is on 150° a value of $^3J_{HCOH}$ =9.8 is reported.[26] The coupling of a 0.005M sample of 8 was 12.1 Hz. Increased concentration resulted in a decrease in coupling constants. This is ascribed to an increase in intermolecular hydrogen bonding perturbing the



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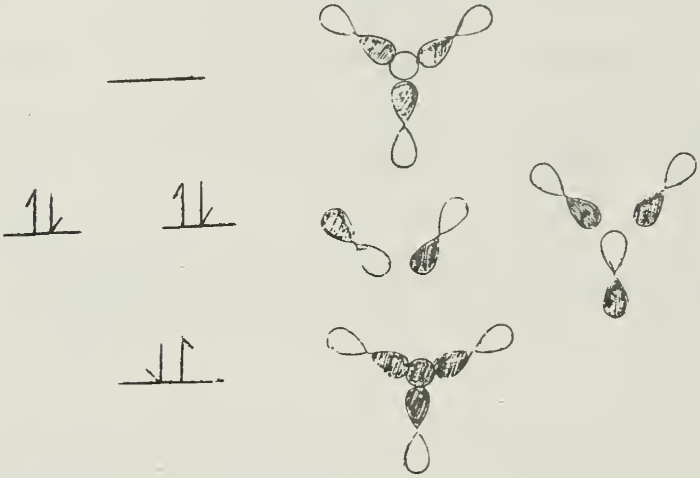
180° dihedral angle. Further comparisons of coupling constants with unsubstituted dioxanes show a difference in values attributable to the expected conformational alterations.

A possible bonding scheme for the electrons about hydrogen is described in Figure 7 .

Figure 7. M.O.'s of a symmetric bifurcated hydrogen



The many parallels in structure and reactivity between hydrogen chemistry and the chemistry of other systems known to involve hypervalent systems are strong evidence for the existence and in many cases the central role of hypervalent hydrogen.

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